Organizacion y Digitalizacion CSA Ltda
CSA851087

08 23022

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Organizacion y
Digitalizacion CSA Ltda

Delegatura de Propiedad Industrial,

División de Nuevas Creciones

SOLICITUD PCT

PATENTE DE INVENCIÓN

(21) **EXPEDIENTE No.** 08-23022

(54) **TÍTULO** AGENTE TERAPEUTICO PARA DIABETES

(51) **CLASIFICACIÓN INTERNACIONAL** A61K 31/44, 31/415

(71) **SOLICITANTE** TAKEDA PHARMACEUTICAL COMPANY LIMITED

DOMICILIO OSAKA, JAPON

(74) **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén

(22) **BOGOTÁ, D C.,**

(FORMA P 10)

08-23022

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-023022- -00000-0000

Fecha: 2008-03-04 16:30:56 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1262

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-023022- -00000-0000
Fecha: 2008-03-04 16:30:56 Dep. 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1262

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**
sociedad constituida y existente bajo las leyes de Japón.

Dirección: 1-1 Doshomachi 4-chome,
Chuo-ku,
Osaka-shi,
Osaka 5410045,
Japón

Domicilio: Osaka,
Japón

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. **Hidenori ABE**
c/o Takeda Pharmaceutical Company Limited,
17-85 Jusohonmachi 2-chome,
Yodogawa-ku,
Osaka-shi,
Osaka 5328686,
Japón

2. **Takeshi WAKABAYASHI**
c/o Takeda Pharmaceutical Company Limited,
17-85 Jusohonmachi 2-chome,
Yodogawa-ku,
Osaka-shi,
Osaka 5328686,
Japón

3. **Kentarou RIKIMARU**
c/o Takeda Pharmaceutical Company Limited,
17-85 Jusohonmachi 2-chome,
Yodogawa-ku,
Osaka-shi,
Osaka 5328686,
Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2006/316068 Fecha: 9 de agosto de 2006
Publicación Internacional No. WO 2007/018314 A3 Fecha: 15 de febrero de 2007

6 Título (54)

AGENTE TERAPEUTICO PARA DIABETES

7 Clasificación Internacional (51) A61K 031/044

8 Prioridad SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	JP	10 de agosto de 2005	2005-232646

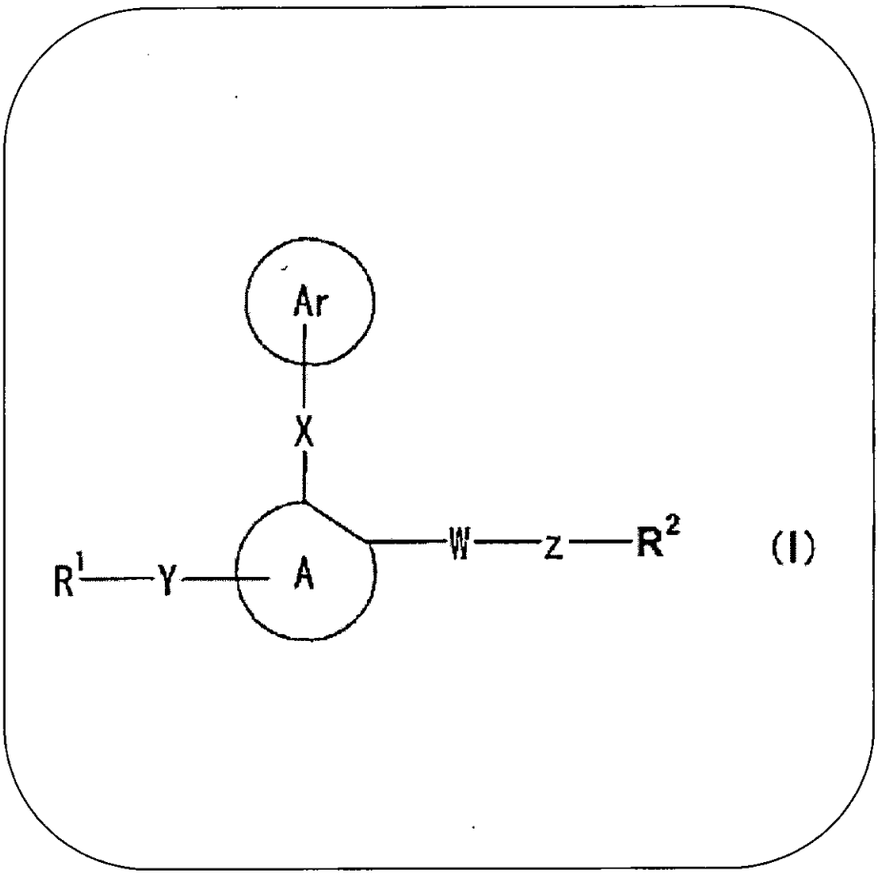
9 **Comprobante de pago No.:** 08-11,298 **Fecha:** 11 de febrero de 2008

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 501.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

AHP

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2007/018314 A3

   Descripción:

   Páginas 497 en el idioma original

   Páginas 721 en español

   Reivindicaciones: Número (s) 21

   Figuras: Número (s) 5

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, D.C. - COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

14656
80852

Yo (nosotros), abajo firmado (s)/I (we), the undersigned
TAKEDA PHARMACEUTICAL COMPANY LIMITED
domiciliado (s) en/of 1-1, Doshomachi 4-chome,
Chuo-ku, Osaka-shi, Osaka Japan

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72_35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso_administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso_administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72_35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above_named attorneys_at_law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin, its renewal, assignment, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights: b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit

DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA CONCUERDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
25 FEB 2008
JUAN MANUEL BOTERO
NOTARIO

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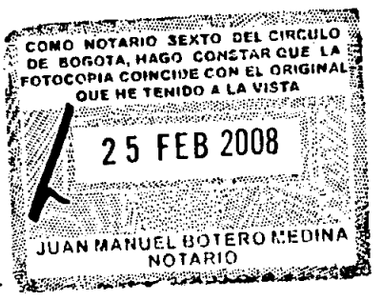
COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
25 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 14th day of December, 2004

en/in Osaka, Japan

por/by

Firma Hiroshi Akimoto Ph. D. Signature
Executive Director
Member of the Board, General Manager,
Intellectual Property Dept.
Authorized Signing Officer

COMO NOTARIO [illegible] TEXTO DEL CIRCULO DE BOGOTA, HA[illegible] CONSTAR QUE LA FOTOCOPIA CO[illegible]CIDE CON EL ORIGINAL QUE HE [illegible]ENIDO A LA VISTA
25 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

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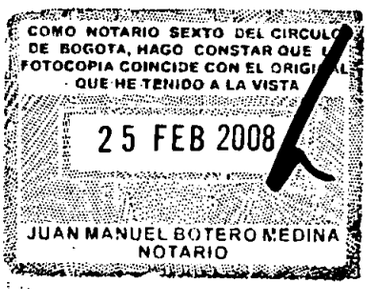

COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE
FOTOCOPIA COINCIDE CON EL ORIGI
QUE HE TENIDO A LA VISTA
25 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

REGISTER NUMBER 334 / 2004

I hereby certify that this document was signed before me and that the signature appearing on the same is the true signature of Hiroshi Akimoto, Ph. D., Executive Director, Member of the Board, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited.

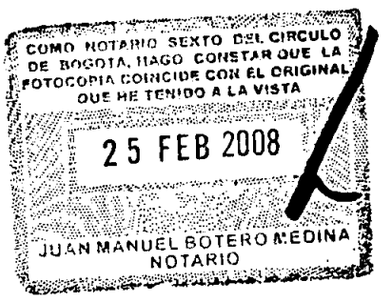
Dated this 14th day of December, 2004

10-8, Edobori 1-chome,
Nishi-ku, Osaka, Japan.

Kiyoomi Fujita

Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau

CONSULADO GENERAL DE JAPON
CONSULADO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
25 FEB 2005
JUAN MANUEL BOTERO MEDINA
NOTARIO


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
25 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

8

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Kiyoomi FUJITA

3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau

4. bears the seal/stamp of — Kiyoomi FUJITA, Notary Public

Certified

5. at **Osaka**

6. DEC. 17. 2004

7. by **the Ministry of Foreign Affairs**

8. No. 04149

9. Seal/stamp:

10. Signature:

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

25 FEB 2008

JUAN MANUEL BOTERO MEDINA
NOTARIO

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGIN
QUE HE TENIDO A LA VISTA

25 FEB 2008

JUAN MANUEL BOTERO MEDINA
NOTARIO

10

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN.
FAX : (06)6944-6248 TEL : (06)6944-~~6412~~ 6411
URL : http://www.osaka.cci.or.jp/

November 17, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

This is to certify that the undermentioned company is registered as a member of this Chamber.

Company name: Takeda Pharmaceutical Company Limited

(The former company name in English was Takeda Chemical Industries, Ltd. until June 29, 2004.)

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Membership Number: KT-01-00080

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

SEMI NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA COPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
25 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

A [illegible]

NO SE AUTORIZA
RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

JEFE DE RELACIONES
EXTERIORES

085749

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

05 FEB 2008

MANUEL BOTERO MEDINA
NOTARIO

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, DICIEMBRE 20, 2004
No. 299

El encargado de las funciones consulares de Colombia

CERTIFICA:

Que el (la) Señor(a) YOSHINOBU KOBAYASHI, quien autoriza el presente documento , es la persona legalmente facultada para representar en la fecha señalada al (a la) CAMARA DE COMERCIO E INDUSTRIA, OSAKA y que la firma y sello que en el documento aparecen como suyos son las que usa y acostumbra para sus actos oficiales.

El Encargado de Funciones Consulares no asume responsabilidad alguna por el contenido del documento.

Firma del Encargado de Funciones Consulares

Derechos: US$23.oo

RAFAEL RICARDO OROZCO
Segundo Secretario

総第 3603 号

証　　明

大阪法務局所属公証人　**藤田清臣**

平成 16 年 12 月 14 日付

平成 16 年 登簿 第 334 号

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

平成 16 年 12 月 17 日
平成　　年　　月　　日

大阪法務局長　**梅津和宏**

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary,duly authorized and practising in Osaka, Japan, and that the Official seal appearing on the same is genuine.

Date 04. 12. 17

Director of the Osaka Legal Affairs Bureau

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, NADO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
28 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

12

TRADUCCIÓN OFICIAL No. 02.04/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento por medio del cual **TAKEDA PHARMACEUTICAL COMPANY LIMIMTED** domiciliado en el 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japón, otorga derechos de Representación y Poder a los Doctores EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PÁEZ, tpa. 23555; y GERMÁN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia.

Dado y firmado el 14 de diciembre de 2004 en Osaka, Japón.

Firma Ilegible

Firma Hiroshi Akimoto Ph. D.
Director Ejecutivo
Miembro de la Junta, Gerente General,
Departamento de Propiedad Intelectual
Signatario Autorizado

REGISTRO NÚMERO **334** / 2004

Por el presente certifico que este documento fue firmado ante mí y que la firma que aparece en el mismo es la firma auténtica de Hiroshi Akimoto, Ph. D., Director Ejecutivo, Miembro de la Junta, Gerente General, Departamento de Propiedad Intelectual de Takeda Pharmaceutical Company Limited.

CONSULADO DE COLOMBIA EN OSAKA
DE BOGOTA, HAGO CONSTAR QUE LA
POTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
25 FEB 2005
JUAN MANUEL BOTERO MEDINA
NOTARIO

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

La Cámara de Comercio e Industria de Osaka

Firma Ilegible

Yoshinobu Kobayashi

Signatario Autorizado

(Respaldo)

Certificado No. 299 del 20 de diciembre de 2004 expedido por la EMBAJADA DE COLOMBIA en Tokio, Japón, en donde se certifica que YOSHINOBU KOBAYASHI está legalmente facultado para firmar a nombre de la Cámara de Comercio e Industria de Osaka y que su firma en el anterior documento es auténtica.

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

Legalización de la firma anterior con el **No. 085749** expedida por el Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Santafe de Bogotá el 4 de febrero de 2005.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-6472/WPCL002G/COLO 14656-845-001-0

Diego F. Vargas

DIEGO F. VARGAS Z.

TRADUCTOR E INTERPRETE OFICIAL

ESPAÑOL - INGLES – INGLES - ESPAÑOL

RES. 0001 DE ENERO 4 DE 1999

MINISTERIO DE JUSTICIA

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

25 FEB 2008

JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Diego Lozano

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 08 FEB 2005

CODEX JURIS CIVILES

REPUBLICA DE COLOMBIA
Juan Manuel Botero Medina
Notario Sexto
SANTAFE DE BOGOTA, D.C.

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:40

JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

313395

Diego Lozano

ESTA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

25 FEB 2008

JUAN MANUEL BOTERO MEDINA
NOTARIO

15

Certificado

5. en **Osaka** 6. DIC 17 DE 2004

7. por el **Ministerio de Relaciones Exteriores**

8. **No. 04149**

DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

9. **Sello/estampilla** 10. **Firma:**

MINISTERIO DE RELACIONES EXTERIORES
JAPÓN

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

LA CÁMARA DE COMERCIO E INDUSTRIA DE OSAKA
2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPÓN
FAX: (06) 6944-6248 TEL: 6944-~~6412~~ 6411
URL: http://www.osaka.cci.or.jp/

Noviembre 17 de 2004

A quién pueda interesar:

CERTIFICADO DE MEMBRESÍA

CONSULADO GENERAL DEL JAPÓN EN BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
25 FEB 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

El presente es para certificar que la siguiente compañía está registrada como miembro de esta Cámara.

Nombre de la compañía: Takeda Pharmaceutical Company Limited

(El nombre anterior de la compañía en inglés fue Takeda Chemical Industries, Ltd. hasta el 29 de junio de 2004.)

Dirección: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japón

Número de Membresía: KT-01-00080

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Diego Fernando Cosgaya

CORRESPONDE CON LA FIRMA INSCRITA Y USADA POR SU (SELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 08 FEB 2005

CODEX JURIS CIVILIS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 FEB 2008

JUAN MANUEL BOTERO MEDINA
NOTARIO

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:39

DIRECCION DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

31839

LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

374

40 16

CESION

Yo, (nosotros) abajo firmado (s)

1.
2.
3.

domiciliado(s) en

1.
2.
3.

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

constituida y existente de conformidad con las leyes de

domiciliada en

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

1. Hidenori ABE
2. Takeshi WAKABAYASHI
3. Kentarou RIKIMARU

of

1. c/o Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8686 Japan
2. same as 1. above
3. same as 1. above

state(s) under oath to be sole and true inventor(s) of the invention:

THERAPEUTIC AGENT FOR DIABETES

state as well, that assign, without reservations or limitations in favour of

TAKEDA PHARMACEUTICAL COMPANY LIMITED

a corporation constituted and existing in conformity with the laws of

JAPAN

domiciled in 1-1 Doshomechi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410045, Japan.

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this

20th day of December 200 7

en/in

Firma/Signature

1. Hidenori ABE Hidenori Abe
2. Takeshi WAKABAYASHI Takeshi Wakabayashi
3. Kentarou RIKIMARU Kentarou Rikimaru

© CAVELIER ABOGADOS

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Masaharu KEMMA

3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau

4. bears the seal/stamp of — Masaharu KEMMA, Notary Public

Certified

5. at **Osaka**

6. DEC. 26. 2007

7. by **the Ministry of Foreign Affairs**

8. No. 5966

9. Seal/stamp:

10. Signature:

Toshihiko TANAKI

For the Minister for Foreign Affairs

大阪法務局所属　公証人役場

認証登簿　平成１９年 第　477　号

嘱託人　阿部秀範、　若林健志、力丸健太郎 は、本職の面前で添付書面に署名した。

よって、これを認証する。

平成　１９　年　１２　月　２０　日

大阪市西区江戸堀１丁目１０番８号

公証人　見　満　正　治　役場において

大阪法務局所属

公証人　見満正治

18

REGISTER NUMBER 477 / 2007

I hereby certify that this document was signed before me and that the signatures appearing on the same are the true signatures of Hidenori ABE, Takeshi WAKABAYASHI and Kentarou RIKIMARU.

Dated this 20th day of December, 2007

10-8, Edobori 1-chome,

Nishi-ku, Osaka, Japan.

Masaharu Kemma

Masaharu KEMMA

Notary attached

to The Osaka Legal

Affairs Bureau

19

総 第 4901 号

証 明

大阪法務局所属公証人 見 満 正 治

平成 19年 12月 20日付

平成19年 登簿 第 477 号

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

平成 平成19年12月26日

大阪法務局長 髙 野 伸

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary,duly authorized and practising in Osaka, Japan, and that the Official Seal appearing on the same is genuine.

Date 07.12.26

Director of the Osaka Legal Affairs Bureau

TRADUCCIÓN OFICIAL No.08.956 de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio del Interior y Justicia, por Resolución No. 323 de 1980 (Se traduce un Documento de Cesión de Inventores a Takeda Pharmaceutical Company Limited Apostilla 5966)

© 374 CESION

cavelier abogados

Yo (Nosotros), abajo firmados: 1.Hidenori ABE

2. Takeshi WAKABAYASHI

3. Kentarou RIKIMARU

Domiciliados en:

1. c/o Takeda Pharmaceutical Company

   17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi

   Osaka 532-8686 Japón

2. Igual al No.1. arriba

3. Igual al No.1, arriba

Declaramos bajo juramento que somos los solos y únicos inventores de la invención:

AGENTE TERAPEUTICO PARA DIABETES.

TRADUCCION OFICIAL No. 08.956
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES. No. 323 DEL MIN. DE JUSTICIA

Igualmente manifestamos bajo juramento, que cedemos, sin reservas ni limitaciones a favor de:

TAKEDA PHARMACEUTICAL COMPANY LIMITED,

Sociedad constituída y existente de conformidad con las leyes de Japón, domiciliada en 1-1 Doshomechi 4- chome, Chuo-ku, Osaka-shi, Osaka 54100045, Japón,

Todos los derechos inherentes a dicha invención y que la arriba mencionada compañía por la presente cesión está capacitada para solicitar, en su nombre la correspondiente invención en la República de Colombia.

Dado y firmado hoy día _____

1. Hidenory ABE (Firma)
2. Takeshi WAKABAYASHI (Firma)
3. Kentarou RIKIMARU

-.-.-.-.-.-

REGISTRO NUMERO 477/2007

Por el presente certifico que este documento fue suscrito ante mí y que Las firmas que aparecen sobre el mismo son las firmas verdaderas de Hidenori ABE, Takeshi WAKABAYASHI y Kentarou RIKIMARU

10-8. Edobori 1-chome,

Nishi-ku, Osaka, Japón

(Firma) Masaharu KEMMA

Notario adjunto a la

Oficina de Asuntos Legales

TRADUCCION OFICIAL No 8-956
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES. No. 323 DEL MIN. DE JUSTICIA

22

De Osaka 4901

C E R T I F I C A D O

Por el presente se certifica que el adjunto Certificado Notarial ha sido suscrito por Notario, debidamente autorizado y en ejercicio en Osaka, Japón, y que el Sello Oficial que aparece sobre el mismo es auténtico.

Fecha 07.12.26

Director de la Oficina de Asuntos Legales de Osaka

© cavelier abogados

wppode01-374

APOSTILLA

(Convención de La Haya del 5 de Octubre 1961)

1. País: Japón
   Este documento Público
2. ha sido suscrito por Masaharu KEMMA
3. obrando en calidad de Notario Público de
   Oficina de Asuntos Legales de Osaka
4. lleva el sello/estampilla de Masaharu KEMMA, Notario Público

Certificada

5 en Osaka 6. Diciembre 26, 2007

7 por el **Ministerio de Relaciones Exteriores**

8 No. **5966**

9 Sello/Estampilla:

10 Firma:

Toshihiko TANAKI

Por el Ministro de Relaciones Exteriores

Es TRADUCCION FIEL Y COMPLETA de la que se deja copia en los archivos de esta oficina y a la cual me remito, habiendo tenido a la vista el documento original. Bogotá, Febrero 20, 2008

Colo 14656-841-032-9 AHP

TRADUCCION OFICIAL No. 08-956
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES. No. 323 DEL MIN. DE JUSTICIA

7 2 9 8 7

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
15 February 2007 (15.02.2007)

(10) International Publication Number
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(51) International Patent Classification:
A61K 31/44 (2006.01) *A61K 31/444* (2006.01)
A61K 31/415 (2006.01) *A61P 3/10* (2006.01)

(21) International Application Number:
PCT/JP2006/316068

(22) International Filing Date: 9 August 2006 (09.08.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2005-232646 10 August 2005 (10.08.2005) JP

(71) Applicant *(for all designated States except US)*: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ABE, Hidenori** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). **WAKABAYASHI, Takeshi** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). **RIKIMARU, Kentarou** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP).

(74) Agent: **TAKASHIMA, Hajime**; Meiji Yasuda Seimei Osaka Midosuji Bldg., 1-1, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410044 (JP).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

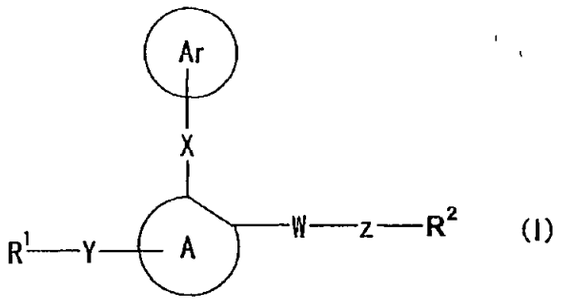
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
5 July 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC AGENT FOR DIABETES



(I)

(57) Abstract: The present invention provides an agent for the prophylaxis or treatment of diabetes, which is associated with a ferwer side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like, and which contains a compound represented by the formula: wherein each symbol is as defined in the specification, or a salt thereof or a prodrug thereof.

WO 2007/018314 A3

1256

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2006/316068

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/44 A61K31/415 A61K31/444 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/072731 A (CEPTOR THERAPEUTICS INC X [US]; BUSCH BRETT [US]; JOHNSON ALAN T [US];) 11 August 2005 (2005-08-11) abstract; claims 54,55; example 69	1-5,7, 9-14, 16-21
P,X	WO 2006/044000 A (DECODE GENETICS [US]; ZHOU NIAN [US]; SINGH JASBIR [US]; GURNEY MARK [) 27 April 2006 (2006-04-27) claims 1,26,29-35; table 1	1-11,13, 14,16,17
X	EP 1 142 879 A1 (FUJISAWA PHARMACEUTICAL CO [JP]) 10 October 2001 (2001-10-10) abstract page 2, paragraph 2 page 6, paragraph 31 - page 10, paragraph 36; examples page 51, paragraph 275; claims	1-7, 9-14, 16-21

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2007	03/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, Philippe

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2006/316068

1257

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 431 267 A1 (ONO PHARMACEUTICAL CO [JP]) 23 June 2004 (2004-06-23) cited in the application claims 1,18; examples 10(1)-10(225)	1-7, 9-14,16, 17
X	WO 00/39077 A (KAROBIO AB [SE]; HANGELAND JON [US]; ZHANG MINSHENG [US]; CARINGAL YOL) 6 July 2000 (2000-07-06) abstract; claims 1,7,8,10,23-29	1-14,16, 17
A	WO 99/47497 A (MERCK FROSST CANADA INC [CA]; GAREAU YVES [CA]; LABELLE MARC [CA]; JUT) 23 September 1999 (1999-09-23) cited in the application abstract; claims; examples	1-21

1258

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/316068

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2006/316068

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2005072731	A	11-08-2005	NONE		
WO 2006044000	A	27-04-2006	NONE		
EP 1142879	A1	10-10-2001	AU	758325 B2	20-03-2003
			AU	1690500 A	31-07-2000
			BR	9917112 A	29-01-2002
			CA	2356838 A1	06-07-2000
			CN	1335837 A	13-02-2002
			CZ	20012338 A3	12-12-2001
			HK	1043791 A1	03-06-2005
			HU	0104657 A2	29-05-2002
			WO	0039097 A1	06-07-2000
			RU	2238937 C2	27-10-2004
			TR	200101865 T2	21-12-2001
			TW	239330 B	11-09-2005
			US	7060721 B1	13-06-2006
EP 1431267	A1	23-06-2004	BR	0211810 A	24-08-2004
			CA	2457468 A1	27-02-2003
			CN	1551866 A	01-12-2004
			HU	0401963 A2	28-01-2005
			WO	03016254 A1	27-02-2003
			MX	PA04001253 A	03-06-2004
			NO	20040564 A	10-05-2004
			NZ	531153 A	28-10-2005
			US	2006258728 A1	16-11-2006
			ZA	200400973 A	04-01-2005
WO 0039077	A	06-07-2000	AU	758202 B2	20-03-2003
			AU	1885500 A	31-07-2000
			BR	9916851 A	16-10-2001
			CA	2356319 A1	06-07-2000
			CN	1337953 A	27-02-2002
			CZ	20012204 A3	14-11-2001
			EP	1144370 A2	17-10-2001
			HU	0104666 A2	28-03-2002
			ID	29013 A	26-07-2001
			JP	2002533432 T	08-10-2002
			NO	20012931 A	21-08-2001
			NZ	512422 A	27-02-2004
			TR	200101834 T2	21-12-2001
			US	2005282872 A1	22-12-2005
			US	6989402 B1	24-01-2006
			ZA	200104932 A	15-01-2003
WO 9947497	A	23-09-1999	AU	2708699 A	11-10-1999
			EP	1071648 A2	31-01-2001

DESCRIPTION

THERAPEUTIC AGENT FOR DIABETES

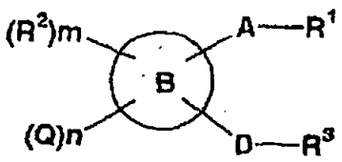
Technical Field

The present invention relates to aromatic compounds useful as therapeutic agents for diabetes.

Background Art

As aromatic compounds, the compounds described in the following literatures are known.

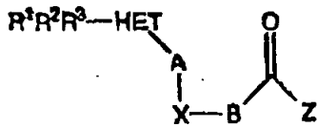
(1) As a therapeutic agent for pain and the like, patent reference 1 (WO2003/016254) describes a compound represented by the formula:



(I)

wherein R^1 is COOH, $COOR^4$ (R^4 is alkyl etc.) and the like; A is alkylene and the like; R^2 is alkyl and the like; m is 0, 1 or 2; B is a benzene ring and the like; Q is alkylene-Cyc2 (Cyc2 is heterocycle etc.), an alkylene-O-benzene ring and the like; n is 0, 1 or 2; D is O-alkylene, NHCO-alkylene and the like; and R^3 is a benzene ring, a naphthalene ring and the like, which has a prostaglandin E2 receptor antagonistic action.

(2) As a therapeutic agent for pain, diabetic retinopathy and the like, patent reference 2 (WO99/47497) describes a compound represented by the formula:



(I)

wherein HET is a 5- to 12-membered monocyclic or bicyclic aromatic ring; R^1, R^2 and R^3 are each independently H, halogen, lower alkyl and the like; A is O, S(O)n and the like; B is $-(C(R^{18})_2)p-Y-(C(R^{18})_2)q-$ (p and q are each independently 0-3); X is a 5- to 10-membered monocyclic aryl group or a heteroaryl group or a bicyclic aryl group or a heteroaryl group having 1-

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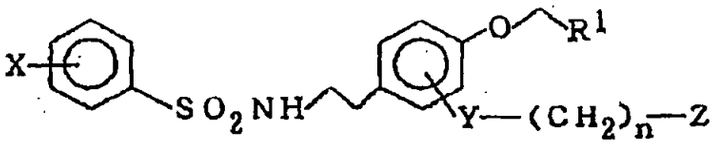
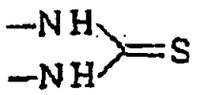
3 hetero atoms selected from O, S(O)n and N(O)m, which is substituted by R^{14} and R^{15} as necessary, (A and B are bonded to the aryl group or heteroaryl group, and are in an ortho position with each other); Y is O, S(O)n, NR^{17}, a bond or -CR^{18}=CR^{18}-; Z is OH or $NHSO_2R^{19}$; R^{17} are each independently H, lower alkyl or Bn; R^{18} are each independently H, F, lower alkyl and the like; R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3, $HET(R^a)_{4-9}$, lower alkyl-$HET(R^a)_{4-9}$ or lower alkynyl-$HET(R^a)_{4-9}$; and R^a is H, OH, halogen, CN, NO_2, amino, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} alkoxy and the like, which is a prostaglandin receptor ligand.

(3) As a therapeutic agent for thrombosis, asthma and the like, patent reference 4 (EP-A-562796) describes a compound represented by the formula:

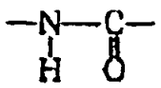


(I)

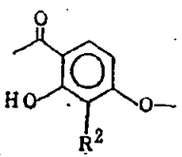
wherein X is a hydrogen atom, a lower alkyl group or a halogen atom; R^1 is a carboxyl group or a lower alkoxycarbonyl group; Y is an oxygen atom,



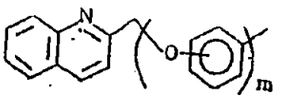
or



; n is an integer of 0-5; Z is



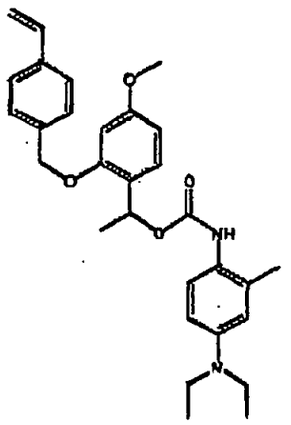
or



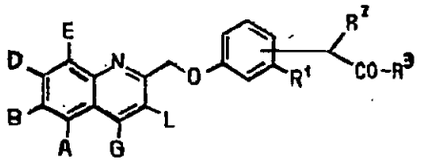
;R^2 is a hydrogen atom or a lower alkyl group; and m is 0 or 1, which is a thromboxane A2 antagonist and a leukotriene antagonist.

(4) As a starting material for a polymer useful as a developing solution (developing agent), patent reference 5

(US-A-2004/137380) describes a compound represented by the formula:

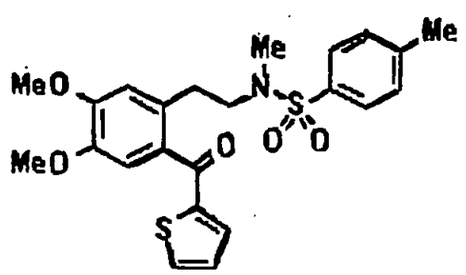


(5) As a therapeutic agent for inflammation, patent reference 6 (US Patent No. 5597833) describes a compound represented by the formula:

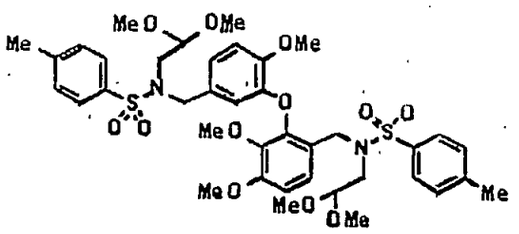


wherein A, B, D, E, G and L are each independently H and the like; R^1 is halogen, not more than C8 alkyl, alkenyl and the like (these are substituted by phenyl etc. as necessary); R^2 is H and the like; R^3 is OH, $NR^4SO_2R^5$ and the like; R^4 is H and the like; R^5 is CF_3, phenyl and the like, which has a 5-lipoxygenase inhibitory action.

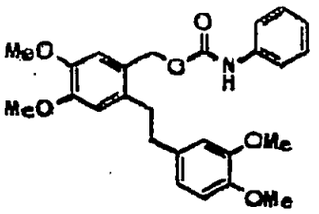
(6) As an intermediate for isoquinoline synthesis, non-patent reference 1 (Perkin Trans, 1, 275 (1985)) describes a compound represented by the formula:



(7) Non-patent reference 2 (Archiv der Pharmazie, 316(6), 694-6 (1983)) describes a compound represented by the formula:



(8) Non-patent reference 3 (Arch Pharm., 141 (1964)) describes a compound represented by the formula:



Peroxisome proliferator-activated receptor gamma (PPARγ), which is one member of the nuclear hormone receptor superfamily represented by steroid hormone receptors and thyroid gland hormone receptors, shows an induced expression at the beginning of differentiation of adipocytes and plays an important role as a master regulator in the differentiation of adipocytes. PPARγ binds to a ligand to form a dimer with retinoid X receptor (RXR), and the dimer binds to a responsive element of a target gene in the nucleus to directly control (activate) the transcription efficiency.

In recent years, a possibility has been suggested that 15-deoxy-Δ12.14 prostaglandin J2, which is a metabolite of prostaglandin D2, is an endogenous ligand of PPARγ, and moreover, it has been clarified that certain insulin sensitizers represented by thiazolidinedione derivatives have a PPARγ ligand activity and the strength of the activity parallels with a hypoglycemic action or adipocyte differentiation promoting action [non-patent reference 4 (Cell, 83, 803 (1995)); non-patent reference 5 (The Journal of Biological Chemistry, 270, 12953(1995)); non-patent reference 6 (Journal of Medicinal Chemistry, 39, 665 (1996))].

It has also been elucidated that 1) PPARγ is expressed in the cultured cell derived from human liposarcoma and the

addition of PPARγ ligand stops its growth [non-patent reference 7 (Proceedings of The National Academy of Sciences of The United States of America, 94, 237 (1997))]; 2) nonsteroidal anti-inflammatory drugs represented by indomethacin and phenoprofen have a PPARγ ligand activity [non-patent reference 8 (The Journal of Biological Chemistry, 272, 3406 (1997))]; 3) PPARγ is highly expressed in activated macrophage, and the addition of its ligand leads to the inhibition of the transcription of the gene involved in inflammation [non-patent reference 9 (Nature, 391, 79 (1998))]; 4) PPARγ ligand inhibits production of inflammatory cytokines by monocyte (TNFα, IL-1β, IL-6) [non-patent reference 10 (Nature, 391, 82 (1998))] and the like.

Disclosure of the Invention

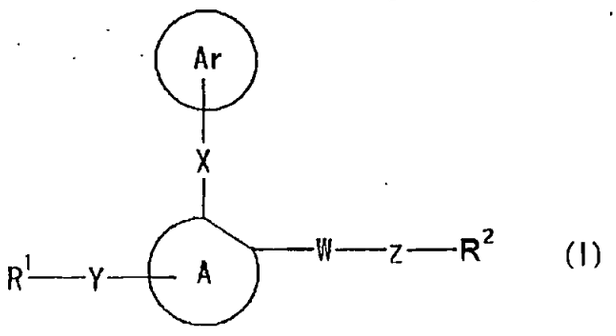
Problems to be Solved by the Invention

There is a demand on the development of an agent for the prophylaxis or treatment of diabetes, which is associated with a fewer side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like.

Means of Solving the Problems

The present inventors have found that a compound represented by the following formula (I) has a superior hypoglycemic action, and is useful for the prophylaxis or treatment of diabetes, which resulted in the completion of the present invention. Accordingly, the present invention relates to the following.

[1] An agent for the prophylaxis or treatment of diabetes, which comprises a compound represented by the formula:



(I)

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wherein ring A is an aromatic ring which is optionally further substituted;

Ar is an optionally substituted monocyclic ring;

R^1 is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a spacer having a main chain of 1 or 2 atoms;

Y is a bond or a spacer having a main chain of 1 or 2 atoms;

W is an optionally substituted divalent hydrocarbon group having 1 to 20 carbon atoms;

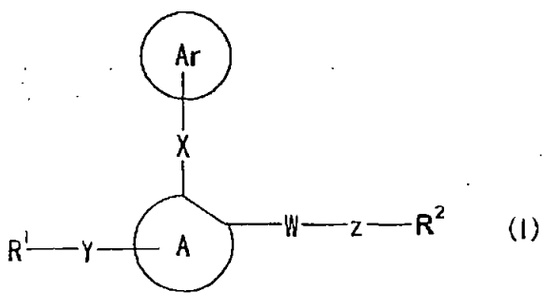
Z is $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$, $-NR^aSO_2NR^bCOO-$ or $-CONR^aSO_2NR^c-$ (R^a and R^b are each independently a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group, R^c is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group, or R^c and R^2 are bonded to each other to form, together with the adjacent nitrogen atom, an optionally substituted, nitrogen-containing heterocycle),

or a salt thereof (hereinafter sometimes to be referred to as compound (I)) or a prodrug thereof.

[2] An insulin sensitizer comprising compound (I) or a prodrug thereof.

[3] The agent of the aforementioned [1], wherein Ar is an optionally substituted monocyclic aromatic ring.

[4] A compound represented by the formula:



(I)

wherein ring A, Ar, R^1, R^2, X, Y, W, Z are as defined in the aforementioned [1] (provided that Ar is not an unsubstituted benzene ring),

or a salt thereof, which excludes the following compounds:

(4-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)-3-{[3-(quinolin-2-ylmethoxy)benzyl]oxy}phenoxy)acetic acid,

ethyl (4-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)-3-{[3-(quinolin-2-ylmethoxy)benzyl]oxy}phenoxy)acetate,

1-{4-methoxy-2-[(4-vinylbenzyl)oxy]phenyl}ethyl [4-(diethylamino)-2-methylphenyl]carbamate,

N-{2-[4,5-dimethoxy-2-(2-thienylcarbonyl)phenyl]ethyl}-N,4-dimethylbenzenesulfonamide,

N-(2,2-dimethoxyethyl)-N-{3-[6-({(2,2-dimethoxyethyl)[(4-methylphenyl)sulfonyl]amino}methyl)-2,3-dimethoxyphenoxy]-4-methoxybenzyl}-4-methylbenzenesulfonamide, and

2-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-dimethoxybenzyl phenylcarbamate.

[5] The compound of the aforementioned [4], wherein Ar is an optionally substituted monocyclic aromatic ring, or a salt thereof.

[6] The compound of the aforementioned [4], wherein Ar is an optionally substituted 5- or 6-membered monocyclic aromatic heterocycle, or a salt thereof.

[7] The compound of the aforementioned [4], wherein Ar is a substituted benzene ring, or a salt thereof.

[8] The compound of the aforementioned [4], wherein X is an oxygen atom, or a salt thereof.

[9] The compound of the aforementioned [4], wherein Z is $-CONR^aSO_2-$, or a salt thereof.

[10] The compound of the aforementioned [4], wherein R^1 is (1) a C_{1-10} alkyl group or a C_{2-10} alkenyl group, each optionally substituted by 1 to 3 substituents selected from

a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group;

a carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group;

an aromatic heterocyclic group optionally substituted by a C_{1-6} alkyl group;

a non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

a C_{1-6} alkoxy-carbonyl group;

a carboxyl group;

a hydroxy group;

a cyano group;

a silyloxy group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and a C_{6-14} aryl group;

a C_{1-6} alkyl-carbonyloxy group;

a C_{3-10} cycloalkyloxy group;

a C_{3-10} cycloalkyl-C_{1-6} alkyloxy group;

a C_{1-6} alkylsulfonyl group;

a C_{1-6} alkyl-carbonyl group; and

a sulfamoyloxy group;

(2) a C_{3-10} cycloalkyl group;

(3) a C_{6-14} aryl group;

(4) a C_{7-13} aralkyl group;

(5) a C_{3-10} cycloalkyl-C_{1-6} alkyl group;

(6) a monocyclic non-aromatic heterocyclic group; or

(7) a monocyclic aromatic heterocyclic group, or a salt thereof.

[11] The compound of the aforementioned [4], wherein R^2 is

(1) a hydrogen atom;

(2) a C_{1-10} alkyl group or a C_{2-10} alkenyl group, each optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group; a halogen atom; a hydroxy group; a cyano group; a C_{1-6} alkylthio group; a carbamoyl group; a C_{6-14} aryloxy group; an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{1-6} alkyl-carbonyl group and a C_{6-14} aryl group; an aromatic heterocyclic group optionally

substituted by 1 to 3 C_{1-6} alkyl group; and a non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

(3) a C_{3-10} cycloalkyl group optionally substituted by a C_{1-6} alkyl group and optionally condensed with a benzene ring;

(4) a C_{6-14} aryl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group, a halogen atom, a nitro group, and a cyano group;

(5) a C_{7-13} aralkyl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group and a C_{6-14} aryl group;

(6) a C_{3-10} cycloalkyl-C_{1-6} alkyl group; or

(7) a non-aromatic heterocyclic group optionally substituted by an oxo group, or a salt thereof.

[12] The compound of the aforementioned [4], wherein ring A is a benzene ring or a 5- or 6-membered aromatic heterocycle, or a salt thereof.

[13] The compound of the aforementioned [4], wherein Y is a bond, -O- or $-SO_2-$, or a salt thereof.

[14] The compound of the aforementioned [4], wherein W is C_{1-6} alkylene or C_{2-6} alkenylene, or a salt thereof.

[15] The compound of the aforementioned [4], which is

3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-(pentylsulfonyl)propanamide,

(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (pentylsulfonyl)carbamate,

3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide,

3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide,

butyl ({2-[3-butoxy -1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate,

(2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(pentylamino)sulfonyl]propanamide,

(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]-N-(pentylsulfonyl)acrylamide or

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate,

or a salt thereof.

[16] A prodrug of the compound of the aforementioned [4] or a salt thereof.

[17] A pharmaceutical agent comprising the compound of the aforementioned [4] or a salt thereof or a prodrug thereof.

[18] A method for the prophylaxis or treatment of diabetes in a mammal, which comprises administering compound (I) or a prodrug thereof to the mammal.

[19] A method of improving insulin resistance in a mammal, which comprises administering compound (I) or a prodrug thereof to the mammal.

[20] Use of compound (I) or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes.

[21] Use of compound (I) or a prodrug thereof for the production of an insulin sensitizer.

Effect of the Invention

According to the present invention, an agent for the prophylaxis or treatment of diabetes, which is associated with a fewer side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like, can be provided.

Brief Description of the Drawings

Fig. 1 shows an X-ray powder diffraction pattern of the crystals obtained in Example 2.

Fig. 2 shows an X-ray powder diffraction pattern of the crystals obtained in Example 12.

Fig. 3 shows an X-ray powder diffraction pattern of the crystals obtained in Example 198.

Fig. 4 shows an X-ray powder diffraction pattern of the crystals obtained in Example 204.

Fig. 5 shows an X-ray powder diffraction pattern of the crystals obtained in Example 208.

Best Mode for Embodying the Invention

The definition of each symbol in the formula (I) is described in detail in the following.

In the present specification, the "halogen atom" is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, unless otherwise specified.

In the present specification, the "C_{1-6} alkyl group" is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like, unless otherwise specified.

In the present specification, the "C_{1-6} alkoxy group" is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like, unless otherwise specified.

In the present specification, the "C_{1-6} alkoxy-carbonyl group" is methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like, unless otherwise specified.

In the present specification, the "C_{1-6} alkyl-carbonyl group" is acetyl, propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, hexanoyl and the like, unless otherwise specified.

R^1 is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group.

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group.

As the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^1 or R^2, for example, a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{4-10} cycloalkadienyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{8-13} arylalkenyl group, a C_{3-10} cycloalkyl-C_{1-6} alkyl group and the like can be mentioned.

As the C_{1-10} alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like can be mentioned.

As the C_{2-10} alkenyl group, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like can be mentioned.

As the C_{2-10} alkynyl group, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like can be mentioned.

As the C_{3-10} cycloalkyl group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl,

bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like can be mentioned.

As the C_{3-10} cycloalkenyl group, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like can be mentioned.

As the C_{4-10} cycloalkadienyl group, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like can be mentioned.

The above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group each may be condensed with a benzene ring, and as such a fused ring group, for example, indanyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl and the like can be mentioned. In addition, crosslinked hydrocarbon groups such as norbornanyl, adamantly and the like can also be mentioned as the aforementioned hydrocarbon group.

As the C_{6-14} aryl group, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenylyl and the like can be mentioned.

As the C_{7-13} aralkyl group, for example, benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl and the like can be mentioned.

As the C_{8-13} arylalkenyl group, for example, styryl and the like can be mentioned.

As the C_{3-10} cycloalkyl-C_{1-6} alkyl group, for example, cyclopropylmethyl, cyclohexylmethyl and the like can be mentioned.

The C_{1-10} alkyl group, C_{2-10} alkenyl group and C_{2-10} alkynyl group exemplified as the aforementioned "hydrocarbon group" optionally has 1 to 3 substituents at substitutable position(s).

As such substituent, for example,

(1) a C_{3-10} cycloalkyl group (e.g., cyclopropyl, cyclohexyl);

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(2) a C_{6-14} aryl group (e.g., phenyl, naphthyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group, a halogen atom and a C_{1-6} alkylsulfonyloxy group (e.g., methylsulfonyloxy);

(3) an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrazolyl, oxadiazolyl, pyrazinyl, quinolyl, indolyl, imidazolyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group and a halogen atom;

(4) a non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, dioxolyl, dioxolanyl, 1,3-dihydro-2-benzofuranyl, thiazolidinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group, an oxo group and a halogen atom;

(5) an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group, a C_{6-14} aryl group (e.g., phenyl), a C_{6-14} aryl-carbonyl group (e.g., benzoyl), a C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl, phenethylcarbonyl), a C_{1-6} alkyl-aminocarbonyl group (e.g., methylaminocarbonyl, ethylaminocarbonyl), a C_{6-14} aryl-aminocarbonyl group (e.g., phenylaminocarbonyl, 1-naphthylaminocarbonyl, 2-naphthylaminocarbonyl), a C_{7-13} aralkyl-aminocarbonyl group (e.g., benzylaminocarbonyl), a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl), a C_{6-14} arylsulfonyl group (e.g., benzenesulfonyl, toluenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl) and a C_{7-13} aralkylsulfonyl group (e.g., benzylsulfonyl);

(6) an amidino group;

(7) a C_{1-6} alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms;

(8) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 halogen atoms;

(9) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl) optionally substituted by 1 to 3 halogen atoms;

(10) a carbamoyl group optionally mono- or di-substituted by substituent(s) selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{6-14} aryl group (e.g., phenyl), a C_{7-13} aralkyl group (e.g., benzyl) and an aromatic heterocycle-C_{1-6} alkyl group (e.g., furfuryl);

(11) a thiocarbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms;

(12) a sulfamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms;

(13) a carboxyl group;

(14) a hydroxy group;

(15) a C_{1-6} alkoxy group optionally substituted by 1 to 3 substituents selected from a halogen atom, a carboxyl group, a C_{1-6} alkoxy group and a C_{1-6} alkoxy-carbonyl group;

(16) a C_{2-6} alkenyloxy group (e.g., ethenyloxy) optionally substituted by 1 to 3 halogen atoms;

(17) a C_{3-10} cycloalkyloxy group (e.g., cyclopropyloxy, cyclohexyloxy);

(18) a C_{7-13} aralkyloxy group (e.g., benzyloxy);

(19) a C_{6-14} aryloxy group (e.g., phenyloxy, naphthyloxy);

(20) a C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, tert-butylcarbonyloxy);

(21) a mercapto group;

(22) a C_{1-6} alkylthio group (e.g., methylthio, ethylthio) optionally substituted by 1 to 3 halogen atoms;

(23) a C_{7-13} aralkylthio group (e.g., benzylthio);

(24) a C_{6-14} arylthio group (e.g., phenylthio, naphthylthio);

(25) a sulfo group;

(26) a cyano group;

(27) an azido group;

(28) a nitro group;

(29) a nitroso group;

(30) a halogen atom;

(31) a C_{1-6} alkylsulfinyl group (e.g., methylsulfinyl);

(32) an oxo group;

(33) a C_{3-10} cycloalkyl-C_{1-6} alkyloxy group (e.g., cyclopropylmethyloxy);

(34) a C_{1-3} alkylenedioxy group (e.g., methylenedioxy, ethylenedioxy);

(35) a hydroxyimino group optionally substituted by a C_{1-6} alkyl group;

(36) a silyloxy group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and a C_{6-14} aryl group (e.g., triisopropylsilyloxy, tert-butyl(diphenyl)silyloxy);

(37) a C_{6-14} aryl-carbonyl group (e.g., benzoyl) optionally substituted by 1 to 3 halogen atoms;

(38) a sulfamoyloxy group;

(39) a carbamoyloxy group;

and the like can be mentioned. When two or more substituents are used, the substituents may be the same or different.

The C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, C_{8-13} arylalkenyl group and C_{3-10} cycloalkyl-C_{1-6} alkyl group exemplified as the aforementioned "hydrocarbon group" optionally have 1 to 3 substituents at substitutable position(s).

As such substituent, for example,

(1) the groups exemplified as the substituents that the aforementioned C_{1-10} alkyl group and the like optionally have;

(2) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a carboxyl group, a hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group,

a C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, tert-butylcarbonyloxy), a carbamoyl group and a non-aromatic heterocyclic group (e.g., piperidino);

(3) a C_{2-6} alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from a halogen atom, a carboxyl group, a hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(4) a C_{7-13} aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group and a halogen atom;

and the like can be mentioned. When two or more substituents are used, the substituents may be the same or different.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^1 or R^2, an aromatic heterocyclic group and a non-aromatic heterocyclic group can be mentioned.

Here, as the aromatic heterocyclic group, for example, a 4- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a condensed aromatic heterocyclic group can be mentioned. As the condensed aromatic heterocyclic group, for example, a group wherein such 4- to 7-membered monocyclic aromatic heterocyclic group and one or two from a 5- or 6-membered ring containing 1 or 2 nitrogen atoms, a 5-membered ring containing one sulfur atom or a benzene ring, and the like are condensed, and the like can be mentioned.

Preferable examples of the aromatic heterocyclic group include monocyclic aromatic heterocyclic groups such as furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl),

pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl) and the like;

condensed aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisooxazolyl (e.g., 7-benzisooxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like; and the like.

As the non-aromatic heterocyclic group, for example, a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a condensed non-aromatic heterocyclic group can be mentioned. As the condensed non-aromatic heterocyclic group, for example, a group wherein such 4- to 7-membered monocyclic non-aromatic heterocyclic group and one or two from a 5- or 6-membered ring containing 1 or 2 nitrogen atoms, a 5-membered ring containing one sulfur atom or a benzene ring, and the like are condensed, and the like can be mentioned.

As preferable examples of the non-aromatic heterocyclic group, monocyclic non-aromatic heterocyclic groups such as oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidinyl (e.g., piperidino, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), 2-thioxo-1,3-oxazolidin-5-yl, pyranyl (e.g., 4-pyranyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-oxidotetrahydrothiopyran-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-

dioxidotetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl), azepanyl (e.g., azepan-3-yl) and the like;

condensed non-aromatic heterocyclic groups such as dihydroindolyl (e.g., 2,3-dihydro-1H-isoindol-1-yl), dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepinyl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl)and the like; and the like can be mentioned.

The "heterocyclic group" of the aforementioned "optionally substituted heterocyclic group" optionally has 1 to 3 substituents at substitutable position(s). As such substituent, for example, those exemplified as the substituents that the C_{3-10} cycloalkyl group and the like exemplified as the "hydrocarbon group" of the aforementioned "optionally substituted hydrocarbon group" may have can be mentioned. When two or more substituents are used, the substituents may be the same or different.

R^1 is preferably

(1) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, tert-butyl) or a C_{2-10} alkenyl group

(preferably 3-butenyl), each optionally substituted by 1 to 3 substituents selected from

a C_{1-6} alkoxy group (preferably methoxy, ethoxy) optionally substituted by a C_{1-6} alkoxy group (preferably methoxy);

a carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group (preferably diethylcarbamoyl);

an aromatic heterocyclic group (preferably pyridyl, oxadiazolyl, furyl) optionally substituted by a C_{1-6} alkyl group;

a non-aromatic heterocyclic group (preferably oxetanyl, pyrrolidinyl, tetrahydrofuryl, dioxolanyl, morpholinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

a C_{1-6} alkoxy-carbonyl group;

a carboxyl group;

a hydroxy group;

a cyano group;

a silyloxy group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and a C_{6-14} aryl group (preferably tert-butyl(diphenyl)silyloxy);

a C_{1-6} alkyl-carbonyloxy group (preferably acetyloxy);

a C_{3-10} cycloalkyloxy group (preferably cyclopropyloxy);

a C_{3-10} cycloalkyl-C_{1-6} alkyloxy group (preferably cyclopropylmethyloxy);

a C_{1-6} alkylsulfonyl group (preferably methylsulfonyl);

a C_{1-6} alkyl-carbonyl group;

a sulfamoyloxy group;

and the like;

(2) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

(3) a C_{6-14} aryl group (preferably phenyl);

(4) a C_{7-13} aralkyl group (preferably benzyl);

(5) a C_{3-10} cycloalkyl-C_{1-6} alkyl group (preferably cyclopropylmethyl);

(6) a monocyclic non-aromatic heterocyclic group (preferably tetrahydropyranyl);

(7) a monocyclic aromatic heterocyclic group (preferably pyrimidinyl);

and the like.

R^1 is more preferably

a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from

a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group; and

a hydroxy group.

R^2 is preferably

(1) a hydrogen atom;

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl) or a C_{2-10} alkenyl group (preferably propenyl), each optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group; a halogen atom; a hydroxy group; a cyano group; a C_{1-6} alkylthio group (preferably methylthio); a carbamoyl group; a C_{6-14} aryloxy group (preferably phenyloxy); an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{1-6} alkyl-carbonyl group and a C_{6-14} aryl group (preferably phenyl); an aromatic heterocyclic group (preferably thienyl, furyl, imidazolyl, pyridyl, pyrazinyl) optionally substituted by 1 to 3 C_{1-6} alkyl group; and a non-aromatic heterocyclic group (preferably tetrahydrofuryl, pyrrolidinyl, morpholinyl, thiomorpholinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

(3) a C_{3-10} cycloalkyl group (preferably cyclohexyl, cyclobutyl, cycloheptyl, indanyl, tetrahydronaphthyl) optionally substituted by a C_{1-6} alkyl group and optionally condensed with a benzene ring;

(4) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a

hydroxy group, a C_{1-6} alkoxy group, a halogen atom, a nitro group, a cyano group and the like;

(5) a C_{7-13} aralkyl group (preferably benzyl, phenethyl, phenylpropyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group and a C_{6-14} aryl group (preferably phenyl);

(6) a C_{3-10} cycloalkyl-C_{1-6} alkyl group (preferably cyclopropylmethyl);

(7) a non-aromatic heterocyclic group (preferably azepanyl) optionally substituted by an oxo group;

and the like.

R^2 is more preferably

a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group; a halogen atom; a hydroxy group; a cyano group; a C_{1-6} alkylthio group (preferably methylthio); a carbamoyl group; a C_{6-14} aryloxy group (preferably phenyloxy); an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{1-6} alkyl-carbonyl group and a C_{6-14} aryl group (preferably phenyl); an aromatic heterocyclic group (preferably thienyl, furyl, imidazolyl, pyridyl, pyrazinyl) optionally substituted by 1 to 3 C_{1-6} alkyl group; and a non-aromatic heterocyclic group (preferably tetrahydrofuryl, pyrrolidinyl, morpholinyl, thiomorpholinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group.

Ring A is an aromatic ring which is optionally further substituted. As the "aromatic ring", for example, aromatic hydrocarbon, aromatic heterocycle and the like can be mentioned. As the aromatic hydrocarbon, for example, a C_{6-14} arene and the like can be mentioned. As the C_{6-14} arene, a ring constituting the C_{6-14} aryl group exemplified as the aforementioned R^1 or R^2 can be mentioned. As the aromatic

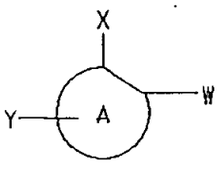
heterocycle, a ring constituting the aromatic heterocyclic group exemplified as the aforementioned R^1 or R^2 can be mentioned. The aromatic ring is preferably a benzene ring, a 5- or 6-membered aromatic heterocycle (preferably pyrazole, pyrrole) and the like.

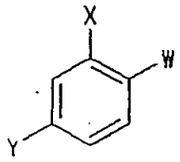
The "aromatic ring" for ring A is substituted by a group -X-, a group -Y- and a group -W-, and optionally further has 1 to 3 substituents at substitutable position(s). As such substituent, those exemplified as the substituents that the C_{3-10} cycloalkyl group and the like exemplified for the aforementioned R^1 or R^2 may have can be mentioned. When two or more substituents are used, the substituents may be the same or different.. The substituent is preferably a C_{1-6} alkyl group.

In the formula (I), the group -X- and the group -W- mean substitution at the ortho position of ring A.

Ring A is preferably a benzene ring or a 5- or 6-membered aromatic heterocycle (preferably pyrazole, pyrrole; more preferably pyrazole), each optionally substituted by a C_{1-6} alkyl group, and the like, more preferably a benzene ring or a 5- or 6-membered aromatic heterocycle (preferably pyrazole, pyrrole; more preferably pyrazole).

When, in the formula (I), ring A is a benzene ring or a pyrazole ring, a partial structural formula



is preferably


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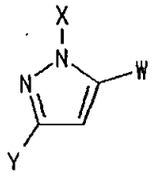

Ar is an "optionally substituted monocyclic ring". Here, the "monocyclic ring" includes a "monocyclic aromatic ring" and a "monocyclic non-aromatic ring". As the "monocyclic aromatic ring", monocyclic rings from among the aromatic hydrocarbons and aromatic heterocycles exemplified as the aforementioned ring A can be mentioned. The monocyclic aromatic ring is preferably a benzene ring, a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine,

pyridazine, oxazole, thiazole) and the like. As the "monocyclic non-aromatic ring", C_{3-10} cycloalkane, C_{3-10} cycloalkene and C_{4-10} cycloalkadiene corresponding to the C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group exemplified as the aforementioned R^1 or R^2, and a monocyclic non-aromatic heterocycle corresponding to the monocyclic non-aromatic heterocyclic group exemplified as the aforementioned R^1 or R^2 (specifically a 5- or 6-membered monocyclic non-aromatic heterocycle containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom; preferably piperidine, tetrahydrofuran) can be mentioned. The monocyclic non-aromatic ring is preferably a C_{3-10} cycloalkane (preferably cyclopropane, cyclohexane), a 5- or 6-membered monocyclic non-aromatic heterocycle (preferably piperidine, tetrahydrofuran) and the like.

Ar is preferably an optionally substituted monocyclic aromatic ring, more preferably a "optionally substituted 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine, pyridazine, oxazole, thiazole; more preferably pyridine)" or a "substituted benzene ring".

The monocyclic ring (monocyclic aromatic ring and monocyclic non-aromatic ring) for Ar optionally has 1 to 3 substituents at substitutable position(s). As such substituent, those exemplified as the substituents that the C_{3-10} cycloalkyl group and the like exemplified as the aforementioned R^1 or R^2 may have can be mentioned.

The substituent of Ar is preferably

(1) a halogen atom;

(2) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably methyl, trifluoromethyl);

(3) a C_{6-14} aryl group (preferably phenyl);

(4) a nitro group;

(5) a carboxyl group;

(6) a C_{1-6} alkyl-carbonyl group (preferably acetyl);

(7) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl, tert-butoxycarbonyl);

(8) a C_{6-14} aryl-carbonyl group (preferably benzoyl);

(9) an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl-carbonyl group (preferably acetyl), a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl, tert-butoxycarbonyl) and C_{1-6} alkylsulfonyl (preferably methylsulfonyl) and the like.

When the monocyclic aromatic ring for Ar is a benzene ring, Ar is preferably a substituted benzene ring.

Ar is preferably

a benzene ring, a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine, pyridazine, oxazole, thiazole), a C_{3-10} cycloalkane (preferably cyclopropane, cyclohexane) and a 5- or 6-membered monocyclic non-aromatic heterocycle (preferably piperidine, tetrahydrofuran), each optionally having 1 to 3 substituents selected from

(1) a halogen atom;

(2) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably methyl, trifluoromethyl);

(3) a C_{6-14} aryl group (preferably phenyl);

(4) a nitro group;

(5) a carboxyl group;

(6) a C_{1-6} alkyl-carbonyl group (preferably acetyl);

(7) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl, tert-butoxycarbonyl);

(8) a C_{6-14} aryl-carbonyl group (preferably benzoyl);

(9) an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl-carbonyl group (preferably acetyl), a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl, tert-butoxycarbonyl) and a C_{1-6} alkylsulfonyl group (preferably methylsulfonyl);

and the like.

Ar is more preferably

a benzene ring or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine) optionally having 1 to 3 substituents selected from

(1) a halogen atom;

(2) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably methyl, trifluoromethyl);

and the like.

X is a spacer having a main chain of 1 or 2 atoms.

As used herein, the "main chain" is a divalent straight chain connecting ring A and ring Ar, and the atom number of the main chain is counted so that the number of atoms in the main chain is minimum. The "main chain" consists of 1 or 2 atoms selected from a carbon atom and a hetero atom (e.g., oxygen atom, sulfur atom, nitrogen atom and the like), and may be saturated or unsaturated. The sulfur atom may be oxidized.

Y is a bond or a spacer having a main chain of 1 or 2 atoms.

As used herein, the "main chain" is a divalent straight chain connecting ring A and the group $-R^1$, and the atom number of the main chain is counted so that the number of atoms in the main chain is minimum. The "main chain" consists of 1 or 2 atoms selected from a carbon atom and a hetero atom (e.g., oxygen atom, sulfur atom, nitrogen atom and the like), and may be saturated or unsaturated. The sulfur atom may be oxidized.

In the "spacer having a main chain of 1 or 2 atoms" for X or Y, the carbon atom and nitrogen atom constituting the main chain optionally have one or more substituents at substitutable position(s). When two or more substituents are used, the substituents may be the same or different.

As the "substituent", those exemplified as the substituents that the C_{3-10} cycloalkyl group and the like exemplified as the aforementioned R^1 or R^2 may have can be mentioned.

Specific examples of the "spacer having a main chain of 1 or 2 atoms" for X or Y include

(1) $-(CH_2)_k-$ wherein k is 1 or 2 (preferably $-CH_2-$, $-CH_2CH_2-$),

(2) $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1 (preferably -O-, $-OCH_2-$, $-CH_2O-$),

(3) $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$ wherein one of k21 and k22 is 0 and the other is 0 or 1, and k23 is an integer of 0 to 3 (preferably -S-, $-SO_2-$, $-SCH_2-$, $-CH_2S-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-SO_3-$),

(4) $-(CH_2)_{k31}-NH-(CH_2)_{k32}-$ wherein one of k31 and k32 is 0 and the other is 0 or 1 (preferably -NH-, $-NHCH_2-$, $-CH_2NH-$) and the like, each optionally substituted by 1 to 3 substituents selected from an oxo group, a C_{1-6} alkyl group etc.

X is preferably $-(CH_2)_k-$, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, $-(CH_2)_{k31}-NH-(CH_2)_{k32}-$ and the like, each optionally substituted by an oxo group, more preferably $-CH_2-$, -O-, $-CH_2O-$, -NH-, -CO-NH- and the like, particularly preferably $-CH_2-$ and -O-. X is particularly preferably -O- (oxygen atom).

Particularly, when Ar is an "optionally substituted 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine)", X is preferably -O-.

When Ar is an "optionally substituted benzene ring (preferably substituted benzene ring)", X is preferably $-CH_2-$.

Y is preferably a bond, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$ and the like, more preferably a bond, -O-, $-SO_2-$, $-SO_3-$ ($-O-SO_2-$ or $-SO_2-O-$) and the like, particularly preferably a bond, -O- or $-SO_2-$. Particularly, -O- is preferable.

As the "divalent hydrocarbon group having 1 to 20 carbon atoms" for W, for example, a "divalent acyclic hydrocarbon group", a "divalent cyclic hydrocarbon group", or a divalent group obtained by combining one or more kinds of "divalent acyclic hydrocarbon groups" and one or more kinds of "divalent cyclic hydrocarbon groups" can be mentioned.

Here, as the "divalent acyclic hydrocarbon group", for example, alkylene having 1 to 20 carbon atoms, alkenylene

having 2 to 20 carbon atoms, alkynylene having 2 to 20 carbon atoms and the like can be mentioned.

As the "divalent cyclic hydrocarbon group", a divalent group and the like obtained by removing any two hydrogen atoms from cycloalkane having 5 to 20 carbon atoms, cycloalkene having 5 to 20 carbon atoms or aromatic hydrocarbon having 6 to 18 carbon atoms (e.g., benzene, naphthalene, indene, anthracene) can be mentioned. Specific examples include 1,2-cyclopentylene, 1,3-cyclopentylene, 1,2-cyclohexylene, 1,3-cyclohexylene, 1,4-cyclohexylene, 1,2-cycloheptylene, 1,3-cycloheptylene, 1,4-cycloheptylene, 3-cyclohexen-1,4-ylene, 3-cyclohexen-1,2-ylene, 2,5-cyclohexadien-1,4-ylene, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,4-naphthylene, 1,6-naphthylene, 2,6-naphthylene, 2,7-naphthylene, 1,5-indenylene, 2,5-indenylene and the like.

The "divalent hydrocarbon group having 1 to 20 carbon atoms" is preferably a divalent hydrocarbon group having 1 to 6 carbon atoms, and

(1) C_{1-6} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-(CH_2)_2CH(CH_3)-$, $-CH_2-CH(CH_3)-CH_2-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-C(CH_3)_2-$);

(2) C_{2-6} alkenylene (e.g., $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, $-CH=C(CH_3)-$, $-CH=C(C_2H_5)-$);

(3) C_{2-6} alkynylene (e.g., $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$)

and the like are especially preferable.

The "divalent hydrocarbon group having 1 to 20 carbon atoms" for W optionally has 1 to 3 substituents at substitutable position(s). As such substituent, for example,

(1) a halogen atom,

(2) a hydroxy group,

(3) a cyano group,

(4) a nitro group,

(5) a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms,

(6) a C_{1-6} alkylthio group optionally substituted by 1 to 3 halogen atoms,

and the like can be mentioned.

W is preferably C_{1-6} alkylene or C_{2-6} alkenylene, each optionally substituted by a C_{1-6} alkoxy group, more preferably C_{1-6} alkylene (preferably $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2-CH(CH_3)-$ or $-CH_2-C(CH_3)_2-$; more preferably $-(CH_2)_2-$ or $-(CH_2)_3-$) or C_{2-6} alkenylene (preferably $-CH=CH-$, $-CH=CH-CH_2-$, $-CH=C(CH_3)-$ or $-CH=C(C_2H_5)-$; more preferably $-CH=CH-$). Particularly, $-(CH_2)_2-$, $-(CH_2)_3-$ and $-CH=CH-$ are preferable.

Z is $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$, $-NR^aSO_2NR^bCOO-$ or $-CONR^aSO_2NR^c-$.

Here, "R^a" and "R^b" are each independently a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group, "R^c" is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group, or R^c and R^2 are bonded to each other to form, together with the adjacent nitrogen atom, an optionally substituted, nitrogen-containing heterocycle".

As the "optionally substituted hydrocarbon group" for R^a, R^b or R^c, those exemplified as the aforementioned R^1 or R^2 can be mentioned.

Of those, a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy group is preferable.

As the "amino-protecting group" for R^a, R^b or R^c, for example, formyl, a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group, a benzoyl group, a C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), a C_{7-14} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), a phthaloyl group, a substituted silyl group (e.g., a tri-C_{1-6} alkyl-silyl group such as trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl and tert-butyldiethylsilyl; tert-

butyldiphenylsily) and the like can be mentioned. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group and nitro group.

As the "nitrogen-containing heterocycle" of the "optionally substituted, nitrogen-containing heterocycle" formed, together with the adjacent nitrogen atom, by R^c and R^2 bonded to each other, for example, a 5- to 7-membered nitrogen-containing heterocycle having, as a ring constituting atom besides carbon atom, at least one nitrogen atom, and further, 1 or 2 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, which is optionally condensed with a benzene ring, can be mentioned. Preferable examples of the nitrogen-containing heterocycle include pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, oxopiperazine, oxopyrrolidine and dihydroisoindoline.

The nitrogen-containing heterocycle optionally have 1 to 3 (preferably 1 or 2) substituents at substitutable position(s). As such substituent, those exemplified as the substituents that the C_{3-10} cycloalkyl group and the like exemplified as the aforementioned R^1 or R^2 may have can be mentioned. Particularly, a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy group, a carbamoyl group and the like are preferable. When two or more substituents are used, the substituents may be the same or different.

R^a and R^b are preferably each independently a hydrogen atom or a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy group, more preferably a hydrogen atom.

R^c is preferably a hydrogen atom or a C_{1-6} alkyl group, or R^c and R^2 are bond to each other to form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle (preferably morpholine, pyrrolidine, piperidine, piperazine, thiomorpholine, oxopyrrolidine, dihydroisoindoline) optionally having 1 to 3 substituents selected from a C_{1-6} alkyl group

optionally substituted by a C_{1-6} alkoxy group and a carbamoyl group.

Z is preferably $-CONR^aSO_2-$, $-SO_2NR^aCOO-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$ or $-CONR^aSO_2NR^c-$, more preferably $-CONR^aSO_2-$ and the like. Z is particularly preferably $-CONHSO_2-$.

Of compounds (I), compounds wherein Ar is not an unsubstituted benzene ring, which are other than the following compounds are novel.

(4-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)-3-{[3-(quinolin-2-ylmethoxy)benzyl]oxy}phenoxy)acetic acid,

ethyl (4-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)-3-{[3-(quinolin-2-ylmethoxy)benzyl]oxy}phenoxy)acetate,

1-{4-methoxy-2-[(4-vinylbenzyl)oxy]phenyl}ethyl [4-(diethylamino)-2-methylphenyl]carbamate,

N-{2-[4,5-dimethoxy-2-(2-thienylcarbonyl)phenyl]ethyl}-N,4-dimethylbenzenesulfonamide,

N-(2,2-dimethoxyethyl)-N-{3-[6-({(2,2-dimethoxyethyl)[(4-methylphenyl)sulfonyl]amino}methyl)-2,3-dimethoxyphenoxy]-4-methoxybenzyl}-4-methylbenzenesulfonamide, and

2-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-dimethoxybenzyl phenylcarbamate

Preferable examples of compound (I) include the following compounds.

[compound AA]

Compound (I) wherein

ring A is a benzene ring, a 5- or 6-membered aromatic heterocycle etc. (preferably pyrazole, pyrrole, more preferably pyrazole), each optionally substituted by a C_{1-6} alkyl group;

Ar is a benzene ring, a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine, pyridazine, oxazole, thiazole), a C_{3-10} cycloalkane (preferably cyclopropane, cyclohexane) and a 5- or 6-membered monocyclic non-aromatic heterocycle (preferably piperidine, tetrahydrofuran), each optionally having 1 to 3 substituents selected from

(1) a halogen atom;

(2) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably methyl, trifluoromethyl);

(3) a C_{6-14} aryl group (preferably phenyl);

(4) a nitro group;

(5) a carboxyl group;

(6) a C_{1-6} alkyl-carbonyl group (preferably acetyl);

(7) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl, tert-butoxycarbonyl);

(8) a C_{6-14} aryl-carbonyl group (preferably benzoyl);

(9) an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl-carbonyl group (preferably acetyl), a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl, tert-butoxycarbonyl) and a C_{1-6} alkylsulfonyl group (preferably methylsulfonyl);

and the like;

R^1 is (1) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, tert-butyl) or a C_{2-10} alkenyl group (preferably 3-butenyl), each optionally substituted by 1 to 3 substituents selected from

a C_{1-6} alkoxy group (preferably methoxy, ethoxy) optionally substituted by a C_{1-6} alkoxy group (preferably methoxy);

a carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group (preferably diethylcarbamoyl);

an aromatic heterocyclic group (preferably pyridyl, oxadiazolyl, furyl) optionally substituted by a C_{1-6} alkyl group;

a non-aromatic heterocyclic group (preferably oxetanyl, pyrrolidinyl, tetrahydrofuryl, dioxolanyl, morpholinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

a C_{1-6} alkoxy-carbonyl group;

a carboxyl group;

a hydroxy group;

a cyano group;

a silyloxy group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and a C_{6-14} aryl group (preferably tert-butyl(diphenyl)silyloxy);

a C_{1-6} alkyl-carbonyloxy group (preferably acetyloxy);

a C_{3-10} cycloalkyloxy group (preferably cyclopropyloxy);

a C_{3-10} cycloalkyl-C_{1-6} alkyloxy group (preferably cyclopropylmethyloxy);

a C_{1-6} alkylsulfonyl group (preferably methylsulfonyl);

a C_{1-6} alkyl-carbonyl group; and

a sulfamoyloxy group;

(2) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

(3) a C_{6-14} aryl group (preferably phenyl);

(4) a C_{7-13} aralkyl group (preferably benzyl);

(5) a C_{3-10} cycloalkyl-C_{1-6} alkyl group (preferably cyclopropylmethyl);

(6) a monocyclic non-aromatic heterocyclic group (preferably tetrahydropyranyl); or

(7) a monocyclic aromatic heterocyclic group (preferably pyrimidinyl);

R^2 is

(1) a hydrogen atom;

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl) or a C_{2-10} alkenyl group (preferably propenyl), each optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group; a halogen atom; a hydroxy group; a cyano group; a C_{1-6} alkylthio group (preferably methylthio); a carbamoyl group; a C_{6-14} aryloxy group (preferably phenyloxy); an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{1-6} alkyl-carbonyl group and a C_{6-14} aryl group (preferably phenyl); an aromatic heterocyclic group (preferably thienyl, furyl, imidazolyl, pyridyl, pyrazinyl) optionally substituted by 1 to 3 C_{1-6} alkyl group; and a non-aromatic heterocyclic group (preferably tetrahydrofuryl,

pyrrolidinyl, morpholinyl, thiomorpholinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

(3) a C_{3-10} cycloalkyl group (preferably cyclohexyl, cyclobutyl, cycloheptyl, indanyl, tetrahydronaphthyl) optionally substituted by a C_{1-6} alkyl group and optionally condensed with a benzene ring;

(4) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group, a halogen atom, a nitro group, a cyano group etc.;

(5) a C_{7-13} aralkyl group (preferably benzyl, phenethyl, phenylpropyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group and a C_{6-14} aryl group (preferably phenyl);

(6) a C_{3-10} cycloalkyl-C_{1-6} alkyl group (preferably cyclopropylmethyl); or

(7) a non-aromatic heterocyclic group (preferably azepanyl) optionally substituted by an oxo group;

X is $-(CH_2)_k-$ wherein k is 1 or 2, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1, or $-(CH_2)_{k31}-NH-(CH_2)_{k32}-$ wherein one of k31 and k32 is 0 and the other is 0 or 1, each optionally substituted by an oxo group;

Y is a bond, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1, or $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$ wherein one of k21 and k22 is 0 and the other is 0 or 1, k23 is an integer of 0 to 3;

W is a C_{1-6} alkylene or a C_{2-6} alkenylene, each optionally substituted by a C_{1-6} alkoxy group;

Z is $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$ or $-CONR^aSO_2NR^c-$;

R^a and R^b are each independently a hydrogen atom or a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy group; and

R^c is a hydrogen atom or a C_{1-6} alkyl group, or R^c and R^2 are bonded to each other to form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle (preferably morpholine, pyrrolidine, piperidine, piperazine, thiomorpholine, oxopyrrolidine, dihydroisoindoline) optionally having 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy group and a carbamoyl group.

[compound A]

Compound (I) wherein

ring A is a benzene ring, a 5- or 6-membered aromatic heterocycle etc. (preferably pyrazole);

Ar is a benzene ring or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine), each optionally having 1 to 3 substituents selected from

(1) a halogen atom;

(2) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably methyl, trifluoromethyl);

and the like;

R^1 is

(1) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, tert-butyl) optionally substituted by a substituent selected from

a C_{1-6} alkoxy group (preferably methoxy);

a carbamoyl group (preferably diethylcarbamoyl) optionally mono- or di-substituted by a C_{1-6} alkyl group;

an aromatic heterocyclic group (preferably pyridyl, oxadiazolyl) optionally substituted by a C_{1-6} alkyl group;

a non-aromatic heterocyclic group (preferably oxetanyl, pyrrolidinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

a C_{1-6} alkoxy-carbonyl group;

a carboxyl group;

etc.;

(2) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

(3) a C_{6-14} aryl group (preferably phenyl);

(4) a C_{7-13} aralkyl group (preferably benzyl);

(5) a C_{3-10} cycloalkyl-C_{1-6} alkyl group (preferably cyclopropylmethyl); or

(6) a monocyclic non-aromatic heterocyclic group (preferably tetrahydropyranyl);

R^2 is

(1) a hydrogen atom;

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl) or a C_{2-10} alkenyl group (preferably propenyl), each optionally substituted by a C_{1-6} alkoxy group;

(3) a C_{3-10} cycloalkyl group (preferably cyclohexyl);

(4) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group, a halogen atom, a nitro group etc.;

(5) a C_{7-13} aralkyl group (preferably benzyl, phenylpropyl); or

(6) a C_{3-10} cycloalkyl-C_{1-6} alkyl group (preferably cyclopropylmethyl);

X is $-(CH_2)_k-$ wherein k is 1 or 2 or $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1;

Y is a bond, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1, or $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$ wherein one of k21 and k22 is 0 and the other is 0 or 1, and k23 is an integer of 0 to 3;

W is C_{1-6} alkylene or C_{2-6} alkenylene;

Z is $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$ or $-CONR^aSO_2NR^c-$;

R^a and R^b are hydrogen atoms; and

R^c is a hydrogen atom or a C_{1-6} alkyl group, or R^c and R^2 are bonded to each other to form, together with the adjacent

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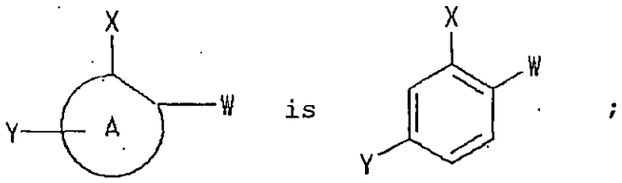
nitrogen atom, a nitrogen-containing heterocycle (preferably morpholine).

[compound B]

Compound (I) wherein

ring A is a benzene ring;



X is $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1;

Y is $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1, or $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$ wherein one of k21 and k22 is 0 and the other is 0 or 1 and k23 is an integer of 0 to 3;

Z is $-CONR^aSO_2-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$ or $-CONR^aSO_2NR^c-$;

R^a is a hydrogen atom;

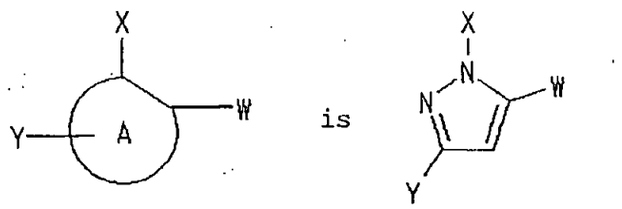
R^c is a hydrogen atom or a C_{1-6} alkyl group, or R^c and R^2 are bonded to each other to form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle (preferably morpholine); and

Ar, R^1, R^2 and W are as defined in the aforementioned [compound A].

[compound C]

Compound (I) wherein

ring A is pyrazole;



X is $-(CH_2)_k-$ wherein k is 1 or 2;

Y is a bond or $-(CH_2)_{k11}-O-(CH_2)_{k12}-$ wherein one of k11 and k12 is 0 and the other is 0 or 1;

Z is $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-OCONR^aSO_2-$ or $-NR^aCONR^bSO_2-$;

R^a and R^b are hydrogen atoms; and

Ar, R^1, R^2 and W are as defined in the aforementioned [compound A].

[compound D]

Compound (I) which is

3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-(pentylsulfonyl)propanamide (Example 2),

(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (Example 12),

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (pentylsulfonyl)carbamate (Example 28),

3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (Example 97),

3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (Example 122),

butyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (Example 129),

(2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (Example 198),

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (Example 204),

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (Example 208),

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(pentylamino)sulfonyl]propanamide (Example 214),

(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]-N-

(pentylsulfonyl)acrylamide (Example 250), or

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (Example 439).

The salts with the compound represented by the formula (I) are preferably pharmacologically acceptable salts and, for example, salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids and the like can be mentioned.

Preferable examples of the salts with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; aluminum salt, ammonium salt and the like.

Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, tromethamine[tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

Preferable examples of the salt with inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Preferable examples of the salt with basic amino acid include a salt with arginine, lysine, ornithine and the like.

Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

The prodrug of the compound (I) is a compound which is converted to the compound (I) with a reaction due to an enzyme,

gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the compound (I) by enzymatic oxidation, reduction, hydrolysis, etc.; a compound which is converted to the compound (I) by hydrolysis etc. due to gastric acid, and the like. A prodrug of the compound (I) may be a compound obtained by subjecting an amino group in the compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in the compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, tetrahydropyranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting a hydroxy group in the compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in the compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, dimethylaminomethylcarbonylation, or tetrahydropyranylation); a compound obtained by subjecting a carboxyl group in the compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in the compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation) and the like. Any of these compounds can be produced from the compound (I) by a method known *per se*.

A prodrug of the compound (I) may be a compound that converts to the compound (I) under physiological conditions as described in Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

The compound (I) may be in the form of a crystal, and the crystal form of the crystal may be single or plural. The crystal can be produced by a crystallization method known *per se*. In the present specification, the melting point means that measured using, for example, a micromelting point apparatus (Yanaco, MP-500D or Buchi, B-545) or a DSC (differential scanning calorimetry) device (SEIKO, EXSTAR6000) and the like.

In general, the melting points vary depending on the measurement apparatuses, the measurement conditions and the like. The crystal in the present specification may show different values from the melting point described in the present specification, as long as they are within a general error range.

The crystal of the compound (I) is superior in physicochemical properties (melting point, solubility, stability etc.) and biological properties (pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression, etc.), and thus it is extremely useful as a medicament.

The compound (I) may be a solvate (e.g., hydrate) or a non-solvate, both of which are encompassed in the compound (I).

A compound labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I) and the like are also encompassed in compound (I).

The compound (I) or a prodrug thereof (hereinafter sometimes to be simply abbreviated as the compound of the present invention) shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, drug interaction, carcinogenicity), and can be used as it is or as a pharmaceutical composition in admixture with a commonly known pharmaceutically acceptable carrier etc., as an agent for the prophylaxis or treatment of the below-mentioned various disease, an insulin sensitizer and the like, in mammals (e.g., humans, mice, rats, rabbits, dogs, cats, bovines, horses, pigs, monkeys).

Here, as the pharmacologically acceptable carrier, various organic or inorganic carrier substances conventionally used as a preparation material can be used. They are incorporated as excipient, lubricant, binder and disintegrant for solid preparations; solvent, dissolution aids, suspending agent, isotonicity agent, buffer and soothing agent for liquid preparations and the like. Where necessary, preparation additives such as preservatives, antioxidants, coloring agents, sweetening agents and the like can be used.

As preferable examples of the excipient, lactose, sucrose, D-mannitol, D-sorbitol, starch, α-starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, magnesium alumino metasilicate and the like can be mentioned.

As preferable examples of the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned.

As preferable examples of the binder, α-starch, saccharose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like can be mentioned.

As preferable examples of the disintegrant, lactose, sucrose, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, light anhydrous silicic acid, low-substituted hydroxypropylcellulose and the like can be mentioned.

As preferable examples of the solvent, water for injection, physiological brine, Ringer solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, cottonseed oil and the like can be mentioned.

As preferable examples of the dissolution aids, polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like can be mentioned.

As preferable examples of the suspending agent, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, polyoxyethylene hydrogenated castor oil, and the like can be mentioned.

As preferable examples of the isotonicity agent, sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose and the like can be mentioned.

As preferable examples of the buffer, buffers such as phosphate, acetate, carbonate, citrate and the like, and the like can be mentioned.

As preferable examples of the soothing agent, benzyl alcohol and the like can be mentioned.

As preferable examples of the preservative, p-oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned.

As preferable examples of the antioxidant, sulfite, ascorbate and the like can be mentioned.

As preferable examples of the coloring agent, water-soluble food tar colors (e.g., food colors such as Food Red Nos. 2 and 3, Food Yellow Nos. 4 and 5, Food Blue Nos. 1 and 2 and the like), water insoluble lake dye (e.g., aluminum salts of the aforementioned water-soluble food tar colors), natural dyes (e.g., β-carotene, chlorophyll, red iron oxide) and the like can be mentioned.

As preferable examples of the sweetening agent, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like can be mentioned.

As the dosage form of the aforementioned pharmaceutical composition, for example, oral preparation such as tablets (including sublingual tablet, orally disintegrating tablet), capsules (including soft capsule, microcapsule), granule, powder, troche, syrup, emulsion, suspension and the like; and parenteral preparation such as injections (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusion), external preparations (e.g., dermal preparation, ointment), suppositories (e.g., rectal suppository, vaginal suppository), pellets, transnasal preparations, pulmonary preparations (inhalant), eye drops and the like can be mentioned. They can be safely administered orally or parenterally.

These preparations may be controlled-release preparations (e.g., sustained-release microcapsule) such as immediate-release preparation, sustained-release preparation and the like.

The pharmaceutical composition can be produced by a method conventionally used in the preparation technical field, such as a method described in the Japanese Pharmacopoeia and the like.

While the content of the compound of the present invention in the pharmaceutical composition varies depending on the dosage form, the dose of the compound of the present invention and the like, it is, for example, about 0.1 to 100 wt%.

The compound of the present invention can be used as an insulin sensitizer, an agent for enhancing insulin sensitivity, a retinoid-related receptor function regulator, a peroxisome proliferator-activated receptor ligand, a retinoid X receptor ligand and the like. The function regulator here means both agonists and antagonists.

The compound of the present invention has a hypoglycemic action, a hypolipidemic action, a blood insulin lowering action, an insulin resistance improving action, an insulin sensitivity enhancing action and a retinoid-related receptor function regulating activity. The function regulator may be a partial agonist or partial antagonist.

Here, the retinoid-related receptors are DNA binding transcription factors included in the nuclear receptors and using a signal molecule such as fat-soluble vitamin and the like as a ligand, which may be monomer receptors, homodimer receptors or heterodimer receptors.

Here, as the monomer receptors, for example, retinoid O receptor (hereinafter sometimes to be abbreviated as ROR) α (GenBank Accession No. L14611), RORβ (GenBank Accession No. L14160), RORγ (GenBank Accession No. U16997); Rev-erb α (GenBank Accession No. M24898), Rev-erb β (GenBank Accession No. L31785); ERRα (GenBank Accession No. X51416), ERRβ (GenBank Accession No. X51417); Ftz-FI α (GenBank Accession No. S65876), Ftz-FI β (GenBank Accession No. M81385); TIx (GenBank Accession No. S77482); GCNF (GenBank Accession No. U14666) and the like can be mentioned.

As the homodimer receptors, for example, homodimers formed by retinoid X receptors (hereinafter sometimes to be abbreviated as RXR) α (GenBank Accession No. X52773), RXRβ (GenBank Accession No. M84820), RXRγ (GenBank Accession No. U38480); COUPα (GenBank Accession No. X12795), COUPβ (GenBank Accession No. M64497), COUPγ (GenBank Accession No. X12794); TR2α (GenBank Accession No. M29960), TR2β (GenBank Accession No. L27586); or HNF4α (GenBank Accession No. X76930), HNF4γ (GenBank Accession No. Z49826) and the like can be mentioned.

As the heterodimer receptors, for example, heterodimers formed by the above-mentioned retinoid X receptors (RXRα, RXRβ or RXRγ) and one kind of receptor selected from retinoid A receptor (hereinafter sometimes to be abbreviated as RAR) α (GenBank Accession No. X06614), RARβ (GenBank Accession No.

Y00291), RARγ (GenBank Accession No. M24857); thyroid gland hormone receptor (hereinafter sometimes to be abbreviated as TR) α (GenBank Accession No. M24748), TRβ (GenBank Accession No. M26747); vitamin D receptor (VDR) (GenBank Accession No. J03258); peroxisome proliferator-activated receptor (hereinafter sometimes to be abbreviated as PPAR) α (GenBank Accession No. L02932), PPARβ (PPARδ) (GenBank Accession No. U10375), PPARγ (GenBank Accession No. L40904); LXRα (GenBank Accession No. U22662), LXRβ (GenBank Accession No. U14534); FXR (GenBank Accession No. U18374); MB67 (GenBank Accession No. L29263); ONR (GenBank Accession No. X75163); and NURα (GenBank Accession No. L13740), NURβ (GenBank Accession No. X75918) and NURγ (GenBank Accession No. U12767) can be mentioned.

The compound of the present invention has a superior ligand activity (activating action) for retinoid X receptors (RXRα, RXRβ, RXRγ) and peroxisome proliferator-activated receptors (PPARα, PPARβ (PPARδ), PPARγ), from among the above-mentioned retinoid-related receptors, and is useful as an agonist, a partial agonist, an antagonist or a partial antagonist of these receptors.

Moreover, the compound of the present invention has a superior ligand activity (activating action) for peroxisome proliferator-activated receptor of heterodimer receptors formed by retinoid X receptor and peroxisome proliferator-activated receptor (e.g., heterodimer receptor formed by RXRα and PPARδ, heterodimer receptor formed by RXRα and PPARγ).

Therefore, the compound of the present invention is preferably used as a peroxisome proliferator-activated receptor ligand or a retinoid X receptor ligand.

The compound of the present invention is useful as a hypoglycemic agent free of side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like.

The compound of the present invention can be used, for example, as an agent for the prophylaxis or treatment of diabetes (e.g., type-1 diabetes, type-2 diabetes, gestational

diabetes, obesity diabetes); an agent for the prophylaxis or treatment of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-HDL-emia, postprandial hyperlipidemia); insulin sensitizer; an agent for enhancing insulin sensitivity; an agent for the prophylaxis or treatment of impaired glucose tolerance [IGT (Impaired Glucose Tolerance)]; and an agent for preventing progress of impaired glucose tolerance into diabetes.

For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria.

According to this report, diabetes is a condition showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, and a non-fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 200 mg/dl. A condition not falling under the above-mentioned diabetes and different from "a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 110 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl" (normal type) is called a "borderline type".

In addition, ADA (American Diabetes Association) and WHO reported new diagnostic criteria of diabetes.

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

According to the above-mentioned reports of ADA and WHO, impaired glucose tolerance is a condition showing a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 140 mg/dl and less than

200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 100 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). On the other hand, WHO defines the IFG (Impaired Fasting Glucose) to be a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 110 mg/dl and less than 126 mg/dl, and calls it IFG (Impaired Fasting Glycaemia).

The compound of the present invention can be also used as an agent for the prophylaxis or treatment of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycaemia), as determined according to the above-mentioned new diagnostic criteria. Moreover, the compound of the present invention can prevent progress of borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycaemia) into diabetes.

The compound of the present invention can also be used as an agent for the prophylaxis or treatment of, for example, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, infectious disease (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder], obesity, osteoporosis, cachexia (e.g., cancerous cachexia, tuberculous cachexia, diabetic cachexia, blood disease cachexia, endocrine disease cachexia, infectious disease cachexia or cachexia due to acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, kidney disease (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage kidney disease),

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muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular accident (e.g., cerebral infarction, cerebral apoplexy), insulin resistance syndrome, Syndrome X, metabolic syndrome (pathology having three or more selected from hypertriglyceridemia (TG), hypoHDL cholesterolemia (HDL-C), hypertension, abdomen overweight and impaired glucose tolerance), hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostate cancer, skin cancer), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., arteriosclerosis (e.g., atherosclerosis), chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis (inclusive of nonalcoholic steatohepatitis), pneumonia, pancreatitis, inflammatory bowel disease, ulcerative colitis, chronic obstructive pulmonary disease (COPD)), visceral obesity syndrome, leg ulcer, sepsis, psoriasis and the like.

In addition, the compound of the present invention can also be used for ameliorating the conditions such as abdominal pain, nausea, vomiting, discomfort in the upper abdomen and the like, which are associated with peptic ulcer, acute or chronic gastritis, biliary dyskinesia, cholecystitis and the like, and the like.

The compound of the present invention can also be used as an agent for the prophylaxis or treatment of inflammatory disease involving TNF-α. Here, the inflammatory disease involving TNF-α is an inflammatory disease developed by the presence of TNF-α, which can be treated via a TNF-α inhibitory effect. As such inflammatory disease, for example, diabetic complications (e.g., retinopathy, nephropathy, neuropathy, macroangiopathy), chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis, pneumonia, stomach

mucous membrane injury (including stomach mucous membrane injury caused by aspirin) and the like can be mentioned.

The compound of the present invention has an apoptosis inhibitory action and can also be used as an agent for the prophylaxis or treatment of diseases involving promotion of apoptosis. As the disease involving promotion of apoptosis, for example, viral diseases (e.g., AIDS, fulminant hepatitis), neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's syndrome, amyotrophic lateral sclerosis, pigmentosa, cerebellar degeneration), myelodysplasia (e.g., aplastic anemia), ischemic diseases (e.g., cardiac infarction, cerebral apoplexy), hepatic diseases (e.g., alcoholic hepatitis, hepatitis B, hepatitis C), joint-diseases (e.g., osteoarthritis), atherosclerosis and the like can be mentioned.

The compound of the present invention can also be used for reduction of visceral fat, inhibition of visceral fat accumulation, glycometabolism improvement, lipometabolism improvement, insulin resistance improvement, oxidized LDL production inhibition, lipoprotein metabolism improvement, coronary metabolism improvement, prophylaxis or treatment of cardiovascular complications, prophylaxis or treatment of heart failure complications, decrease of blood remnant, prophylaxis or treatment of anovulation, prophylaxis or treatment of hirsutism, prophylaxis or treatment of hyperandrogenemia and the like.

The compound of the present invention can also be used as secondary prevention and suppression of progression of the above-mentioned various diseases (e.g., cardiovascular event such as cardiac infarction and the like).

While the dose of the compound of the present invention varies depending on the administration subject, administration route, target disease, condition and the like, for example, it is generally about 0.005 to 50 mg/kg body weight, preferably 0.01 to 2 mg/kg body weight, more preferably 0.025 to 0.5 mg/kg body weight, for oral administration to adult diabetic

patients, which is desirably administered in one to three portions a day.

The compound of the present invention can be used in combination with pharmaceutical agents (hereinafter to be abbreviated as combination drug) such as therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents, antiobesity agents, diuretics, chemotherapeutic agents, immunotherapeutic agents, antithrombotic agents, therapeutic agents for osteoporosis, antidementia agents, erectile dysfunction ameliorating agents, therapeutic agents for urinary incontinence or pollakiuria, therapeutic agents for dysuria and the like. These combination drugs may be low-molecular-weight compounds, or high-molecular-weight protein, polypeptide, antibody, vaccine and the like.

The administration time of the compound of the present invention and the combination drug is not restricted, and these can be administered to an administration subject simultaneously, or may be administered at staggered times.

As the administration mode of the compound of the present invention and the combination drug, the following methods can be mentioned: (1) The compound of the present invention and the combination drug are simultaneously formulated to give a single preparation which is administered. (2) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered by the same administration route at staggered times. (4) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered simultaneously by the different administration routes. (5) The compound of the present invention and the combination drug are

separately formulated to give two kinds of preparations which are administered by the different administration routes at staggered times (for example, the compound of the present invention and the combination drug are administered in this order, or in the reverse order), and the like.

The dose of the combination drug can be appropriately determined based on the dose employed clinically.

The mixing ratio of the compound of the present invention and a combination drug can be appropriately determined depending on the administration subject, administration route, target disease, symptom, combination and the like. When the administration subject is human, for example, a combination drug can be used in 0.01 to 100 parts by weight relative to 1 part by weight of the compound of the present invention.

As the therapeutic agents for diabetes, insulin preparations (e.g., animal insulin preparations extracted from pancreas of bovine and swine; human insulin preparations genetically synthesized using *Escherichia coli*, yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1), oral insulin preparation), insulin sensitizers (e.g., pioglitazone or a salt thereof (preferably hydrochloride), rosiglitazone or a salt thereof (preferably maleate), Netoglitazone, Rivoglitazone (CS-011), FK-614, the compound described in WO01/38325, Tesaglitazar (AZ-242), Ragaglitazar (NN-622), Muraglitazar (BMS-298585), Edaglitazone (BM-13-1258), Metaglidasen (MBX-102), Naveglitazar (LY-519818), MX-6054, LY-510929, AMG-131(T-131), THR-0921), α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate etc.), biguanides (e.g., phenformin, metformin, buformin or a salt thereof (e.g., hydrochloride, fumarate, succinate)), insulin secretagogues [sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or calcium salt hydrate thereof], dipeptidyl peptidase IV inhibitors

(e.g., Vidagliptin (LAF237), P32/98, Sitagliptin (MK-431), P93/01, PT-100, Saxagliptin (BMS-477118), T-6666, TS-021), β3 agonists (e.g., AJ-9677), GPR40 agonists, GLP-1 receptor agonists [e.g., GLP-1, GLP-1MR agent, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH_2, CJC-1131], amylin agonists (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists), SGLUT (sodium-glucose cotransporter) inhibitors (e.g., T-1095), 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498), adiponectin or agonists thereof, IKK inhibitors (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists (compounds described in WO01/25228, WO03/42204, WO98/44921, WO98/45285, WO99/22735 etc.), glucokinase activators (e.g., Ro-28-1675), GIP (Glucose-dependent insulinotropic peptide) and the like can be mentioned.

Examples of the therapeutic agents for diabetic complications include aldose reductase inhibitors (e.g., Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat, CT-112, ranirestat (AS-3201)), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF, neurotrophin production-secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole), PKC inhibitors (e.g., ruboxistaurin mesylate)), AGE inhibitors (e.g., ALT946, pimagedine, N-phenacylthiazolium bromide (ALT-766), EXO-226, Pyridorin, Pyridoxamine), active oxygen scavengers (e.g., thioctic acid), cerebral vasodilators (e.g., tiapuride, mexiletine), somatostatin receptor agonist (e.g., BIM23190), apoptosis signal regulating kinase-1 (ASK-1) inhibitors and the like.

Examples of the therapeutic agents for hyperlipidemia include HMG-CoA reductase inhibitors (e.g., pravastatin,

simvastatin, lovastatin, atorvastatin, fluvastatin, rosuvastatin, pitavastatin or a salt thereof (e.g., sodium salt, calcium salt)), squalene synthase inhibitors (e.g., compounds described in WO97/10224, such as N-[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic acid), fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate), ACAT inhibitors (e.g., Avasimibe), Eflucimibe)), anion exchange resins (e.g., colestyramine), probucol, nicotinic acid drugs (e.g., nicomol, niceritrol)), ethyl icosapentate, plant sterol (e.g., soysterol), γ-oryzanol) and the like.

Examples of the antihypertensive agents include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril), angiotensin II antagonists (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, olmesartan medoxomil, tasosartan, 1-[[2'-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1H-benzimidazole-7-carboxylic acid), calcium channel blockers (e.g., manidipine, nifedipine, nicardipine, amlodipine, efonidipine), potassium channel openers (e.g., levcromakalim, L-27152, AL0671, NIP-121), clonidine and the like.

Examples of the antiobesity agents include antiobesity agents acting on the central nervous system (e.g., dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex; MCH receptor antagonists (e.g., SB-568849; SNAP-7941; compounds described in WO01/82925 and WO01/87834); neuropeptide Y antagonists (e.g., CP-422935); cannabinoid receptor antagonists (e.g., SR-141716, SR-147778); ghrelin antagonists; 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498)), pancreatic lipase inhibitors (e.g., orlistat, cetilistat (ATL-962)), β3 agonists (e.g., AJ-9677), peptide anorexiants (e.g., leptin, CNTF (Ciliary Neurotropic Factor)),

cholecystokinin agonists (e.g., lintitript, FPL-15849), feeding deterrents (e.g., P-57) and the like.

Examples of the diuretics include xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide), antialdosterone preparations (e.g., spironolactone, triamterene), carbonate dehydratase inhibitors (e.g., acetazolamide), chlorobenzenesulfonamide preparations (e.g., chlortalidone, mefruside, indapamide), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like.

Examples of the chemotherapeutic agents include alkylating agents (e.g., cyclophosphamide, ifosfamide), metabolic antagonists (e.g., methotrexate, 5-fluorouracil and a derivative thereof), antitumor antibiotics (e.g., mitomycin, adriamycin), plant-derived antitumor agent (e.g., vincristine, vindesine, Taxol), cisplatin, carboplatin, etoposide and the like. Of these, Furtulon or NeoFurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

Examples of the immunotherapeutic agents include microorganism or bacteral components (e.g., muramyl dipeptide derivative, Picibanil), polysaccharides having immunity potentiating activity (e.g., lentinan, schizophyllan, krestin), cytokines obtained by genetic engineering techniques (e.g., interferon, interleukin (IL)), colony stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin) and the like, with preference given to interleukins such as IL-1, IL-2, IL-12 and the like.

Examples of the antithrombotic agents include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium), warfarin (e.g., warfarin potassium), anti-thrombin drugs (e.g., aragatroban), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), platelet

aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride) and the like.

Examples of the therapeutic agents for osteoporosis include alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone, risedronate disodium, pamidronate disodium, alendronate sodium hydrate, incadronate disodium and the like.

Examples of the antidementia agents include tacrine, donepezil, rivastigmine, galanthamine and the like.

Examples of the erectile dysfunction ameliorating agents include apomorphine, sildenafil citrate and the like.

Examples of the therapeutic agents for urinary incontinence or pollakiuria include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like.

Examples of the therapeutic agents for dysuria include acetylcholine esterase inhibitors (e.g., distigmine) and the like.

Examples of the combination drugs include drugs having a cachexia-ameliorating action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., indomethacin), progesterone derivatives (e.g., megestrol acetate), glucosteroids (e.g., dexamethasone), metoclopramide agents, tetrahydrocannabinol agents, fat metabolism improving agents (e.g., eicosapentanoic acid), growth hormones, IGF-1, or antibodies to a cachexia-inducing factor such as TNF-α, LIF, IL-6, oncostatin M and the like.

As the combination drugs, nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide), antidepressants (e.g., desipramine, amitriptyline, imipramine), antiepileptics (e.g., lamotrigine), antiarrhythmic agents (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), narcotic analgesics (e.g.,

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morphine), GABA receptor agonists (e.g., gabapentin), α2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), antianxiety drugs (e.g., benzothiazepines), dopamine receptor agonists (e.g., apomorphine), midazolam, ketoconazole and the like can also be mentioned.

The combination drug is preferably an insulin preparation, an insulin sensitizer, an α-glucosidase inhibitor, biguanide, insulin secretagogue (preferably sulfonylurea) and the like.

The above-mentioned combination drugs may be used in a mixture of two or more kinds thereof at an appropriate ratio.

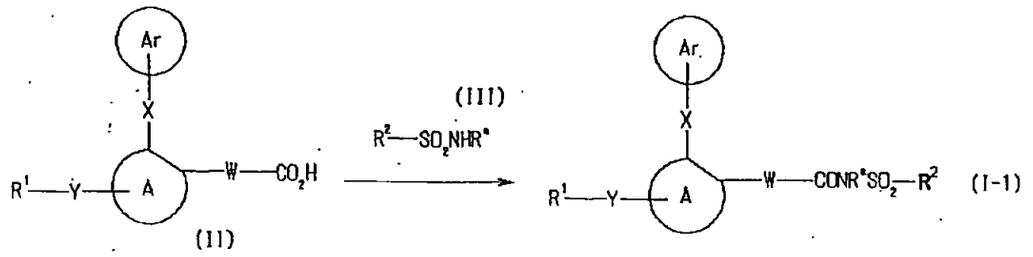
When the compound of the present invention is used in combination with a combination drug, the dose of each agent can be reduced within a safe range in consideration of the side effects thereof. Particularly, the doses of insulin sensitizers, insulin secretagogues and biguanides can be reduced from generally dose levels. Therefore, the side effects possibly caused by these agents can be safely prevented. In addition, the doses of the therapeutic agents for diabetic complications, the therapeutic agents for hyperlipidemia and the antihypertensive agents can be reduced, and as a result, the side effects possibly caused by these agents can be effectively prevented.

The production method of the compound of the present invention is explained in the following.

Compound (I) can be produced by a method known *per se*, for example Method A to Method L, Method R shown below or a method analogous thereto. In the following respective production methods, the starting material compound may be used as a salt, and as such salt, those exemplified as the salts of the compound represented by the formula (I) can be used.

Compound (I-1) of the formula (I) wherein Z is $-CONR^aSO_2-$ (R^a is as defined above) can be produced, for example, by the following Method A.

[Method A]



wherein the symbols in the formula are as defined above.

In the present method, compound (I-1) is produced by subjecting compound (II) to an amidation reaction. This reaction is carried out by a method known *per se*, for example, a method including directly condensing compound (II) with compound (III), or a method including reacting a reactive derivative of compound (II) with compound (III) and the like. Here, as the reactive derivative of compound (II), for example, acid anhydride, acid halide (e.g., acid chloride, acid bromide), imidazolide, mixed acid anhydride (e.g., anhydride with methyl carbonate, ethyl carbonate, isobutyl carbonate, 2,4,6-trichlorobenzoic acid or 2-methyl-6-nitrobenzoic acid) and the like can be mentioned.

The method including directly condensing compound (II) with compound (III) is carried out in the presence of a condensation agent, in a solvent that does not adversely influence the reaction.

As the condensation agent, for example, generally known condensation agents such as carbodiimide condensation reagents (e.g., dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-dimethylaminopropylcarbodiimide and hydrochloride thereof); phosphoric acid condensation reagents such as diethyl cyanophosphate, diphenylphosphoryl azide and the like; N,N'-carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate, chlorodimethoxytriazine and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic

hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (III) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (II).

The amount of the condensation agent to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (II).

When a carbodiimide condensation reagent is used as the condensation agent, a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide) is used as necessary to improve the reaction efficiency. When a phosphoric acid condensation reagent is used as the condensation agent, an organic amine base such as triethylamine, diisopropylethylamine and the like is generally added to improve the reaction efficiency.

The amount of the above-mentioned condensation promoter and the organic amine base to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (II).

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 60 hr.

In a method using a reactive derivative of compound (II), when, for example, acid halide is used as the reactive derivative of compound (II), the reaction is carried out in the presence of a base in a solvent that does not adversely influence the reaction.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate,

potassium carbonate and the like; and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like, ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (III) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (II).

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

When mixed acid anhydride is used as the reactive derivative of compound (II), compound (II) is reacted with any of chlorocarbonate (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate), acid chloride (e.g., 2,4,6-trichlorobenzoyl chloride) and acid anhydride (e.g., 2,4,6-trichlorobenzoic acid anhydride, 2-methyl-6-nitrobenzoic acid anhydride) in the presence of a base (e.g., amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like), and then reacted with compound (III).

The amount of compound (III) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (II).

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

When imidazolide is used as the reactive derivative of compound (II), compound (II) is reacted with N,N'-carbonyldiimidazole and further reacted with compound (III) in

the presence of a base (e.g., amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like).

The amount of compound (III) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (II).

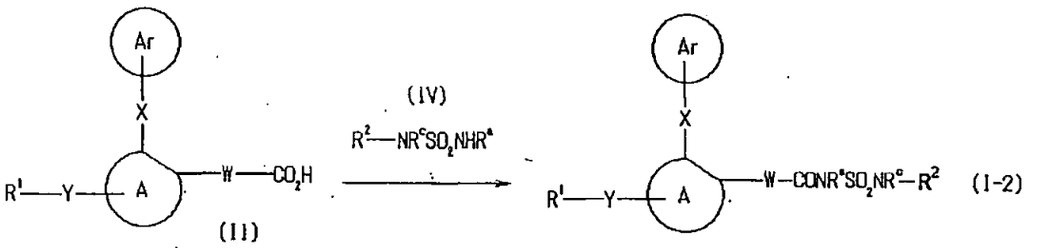
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

Compound (III) to be used as a starting material compound in the above-mentioned Method A can be produced according to a method known *per se*.

Compound (I-2) of the formula (I) wherein Z is -$CONR^aSO_2NR^c$- (R^a and R^c are as defined above) can be produced, for example, by the following Method B.

[Method B]



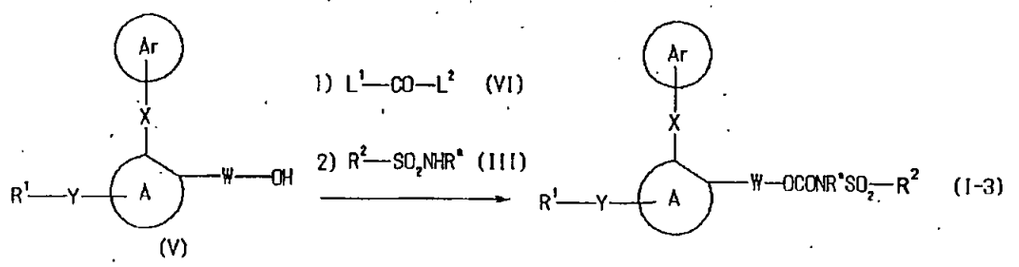
wherein the symbols in the formula are as defined above.

In the present method, compound (II) is reacted with compound (IV) to give compound (I-2). This reaction is carried out in the same manner as in the amidation reaction in the aforementioned Method A.

Compound (IV) can be produced according to a method known *per se*.

Compound (I-3) of the formula (I) wherein Z is -$OCONR^aSO_2$- (R^a is as defined above) can be produced, for example, by the following Method C or Method D.

[Method C]



wherein L^1 and L^2 are the same or different and each is a leaving group, and other symbols are as defined above.

Here, as the leaving group for L^1 or L^2, for example, a hydroxy group, a halogen atom, imidazolyl group, a succinimidooxy group or $-OSO_2R^3$ (R^3 is an alkyl group having 1 to 4 carbon atoms, an aryl group having 6 to 10 carbon atoms optionally substituted by an alkyl group having 1 to 4 carbon atoms) and the like can be mentioned.

As the alkyl group having 1 to 4 carbon atoms of the "alkyl group having 1 to 4 carbon atoms" and the "aryl group having 6 to 10 carbon atoms optionally substituted by an alkyl group having 1 to 4 carbon atoms" for R^3, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl can be mentioned, with preference given to methyl.

As the aryl group having 6 to 10 carbon atoms of the "aryl group having 6 to 10 carbon atoms optionally substituted by an alkyl group having 1 to 4 carbon atoms" for R^3, for example, phenyl and naphthyl can be mentioned, with preference given to phenyl.

R^3 is particularly preferably methyl, tolyl and the like.

In the present method, compound (I-3) is produced from compound (V). This reaction is carried out by a method known *per se*, for example, by reacting compound (V) with compound (VI) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 5 hr, and reacting the obtained compound with compound (III) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 24 hr. Where necessary, this reaction may be carried out in the presence of about 1 to 5 equivalents of a base.

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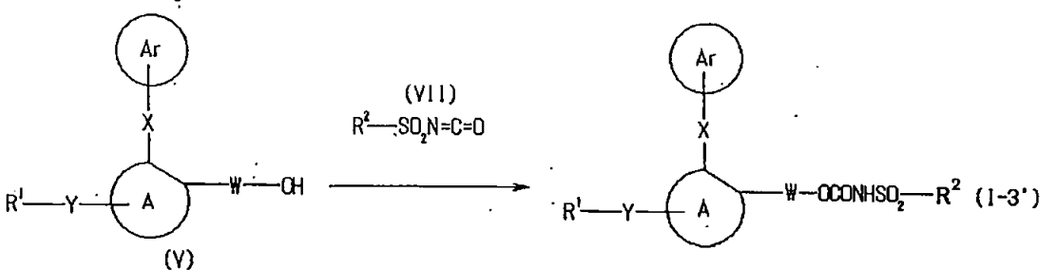
As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (VI) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

The amount of compound (III) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

[Method D]



wherein the symbols in the formula are as defined above.

In the present method, compound (V) is reacted with compound (VII) to give, from among compounds (I-3), compound (I-3') wherein R^a is a hydrogen atom. This reaction is carried out by a method known per se, for example, by reacting compound (V) with compound (VII) in a solvent that does not adversely influence the reaction. Where necessary, this

reaction may be carried out in the presence of about 1 to 5 equivalents of a base.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, pyridine, ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (VII) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

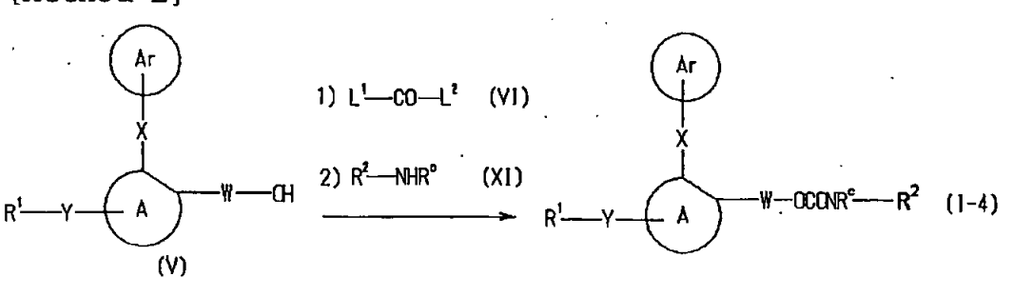
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

Compound (VII) to be used as a starting material compound in the above-mentioned Method D can be produced according to a method known *per se*.

Compound (I-4) of the formula (I) wherein Z is $-OCONR^c-$ (R^c is as defined above) can be produced, for example, by the following Method E.

[Method E]



wherein the symbols in the formula are as defined above.

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In the present method, compound (I-4) is produced from compound (V). This reaction is carried out by a method known *per se*, for example, by reacting compound (V) with compound (VI) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 5 hr, and reacting the obtained compound with compound (XI) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 24 hr. Where necessary, this reaction may be carried out in the presence of about 1 to 5 equivalents of a base.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

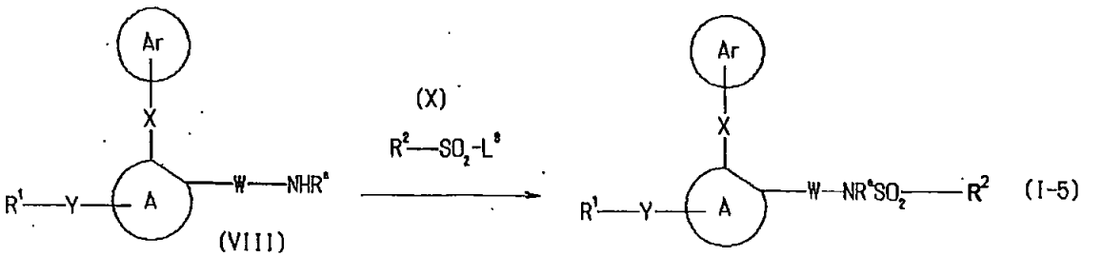
The amount of compound (VI) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

The amount of compound (XI) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

Compound (XI) to be used as a starting material compound in the above-mentioned Method E can be produced according to a method known *per se*.

Compound (I-5) of the formula (I) wherein Z is $-NR^aSO_2-$ (R^a is as defined above) can be produced, for example, by the following Method F or G.

[Method F]



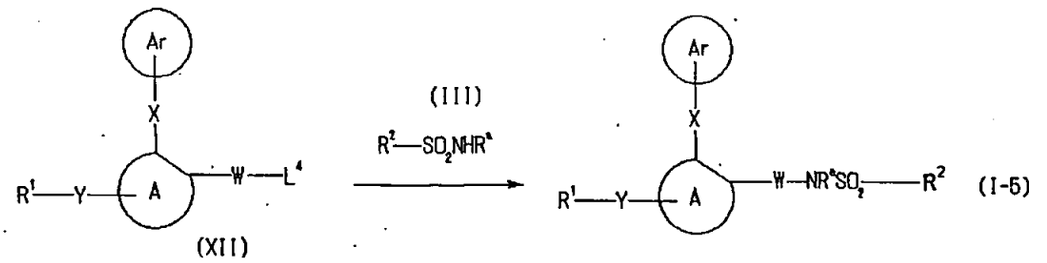
wherein L^3 is a leaving group, and other symbols are as defined above.

As the "leaving group" for L^3, those exemplified as the aforementioned L^1 and L^2 can be mentioned. Of those, a halogen atom is preferable and a chlorine atom is particularly preferable.

In the present method, compound (VIII) is reacted with compound (X) to give compound (I-5). This reaction is carried out in the same manner as in the amidation reaction in the aforementioned Method A.

Compound (X) to be used as a starting material compound in the above-mentioned Method F can be produced according to a method known *per se*.

[Method G]



wherein L^4 is a leaving group, and other symbols are as defined above.

As the "leaving group" for L^4, those exemplified as the aforementioned L^1 and L^2 can be mentioned. Of those, a halogen atom and $-OSO_2R^3$ are preferable and a chlorine atom and a methanesulfonyloxy group are particularly preferable.

In the present method, compound (XII) is reacted with compound (III) to give compound (I-5).

When L^4 is a hydroxy group, this reaction is carried out by a method known *per se*, for example, the method described in Synthesis, page 1 (1981), or a method analogous thereto. In other words, this reaction is generally carried out in the presence of an organic phosphorus compound and an electrophilic agent in a solvent that does not adversely influence the reaction.

As the organic phosphorus compound, for example, triphenylphosphine, tributylphosphine and the like can be mentioned.

As the electrophilic agent, for example, diethyl azodicarboxylate, diisopropyl azodicarboxylate, 1,1'-azodicarbonyldipiperidine and the like can be mentioned.

The amounts of the organic phosphorus compound and the electrophilic agent to be used are preferably about 1 to about 5 molar equivalents relative to compound (XII).

The amount of compound (III) to be used is preferably about 1 to about 5 molar equivalents relative to compound (XII).

As the solvent that does not adversely influence the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

When L^4 is a halogen atom or $-OSO_2R^3$, this reaction is carried out according to a conventional method in the presence

of a base in a solvent that does not adversely influence the reaction.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents, relative to compound (XII).

The amount of compound (III) to be used is preferably about 1 to about 5 molar equivalents, relative to compound (XII).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

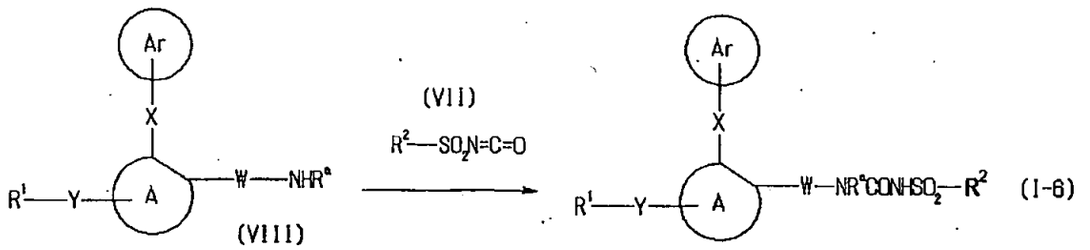
The reaction time is generally about 0.5 to about 20 hr.

Compound (XII) used as the starting material compound in the above-mentioned Method G can be produced by a method known *per se* from the aforementioned compound (V).

Compound (I-6) of the formula (I) wherein Z is $-NR^aCONR^bSO_2-$ (R^a and R^b are as defined above), and R^b is a

hydrogen atom can be produced, for example, by the following Method H.

[Method H]

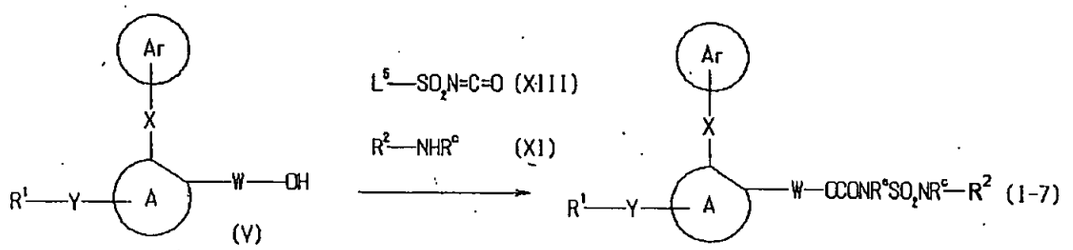


wherein the symbols in the formula are as defined above.

In the present method, compound (VIII) is reacted with compound (VII) to give compound (I-6). This reaction is carried out in the same manner as in the aforementioned Method D.

Compound (I-7) of the formula (I) wherein Z is -$OCONR^aSO_2NR^c$- (R^a and R^c are as defined above) can be produced, for example, by the following Method I.

[Method I]



wherein L^5 is a leaving group, and other symbols are as defined above.

As the "leaving group" for L^5, those exemplified as the aforementioned L^1 and L^2 can be mentioned. Of those, a halogen atom is preferable and a chlorine atom is particularly preferable.

In the present method, compound (I-7) is produced from compound (V). This reaction is carried out by a method known *per se*, for example, by reacting compound (V) with compound (XIII) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 5 hr, and reacting the obtained compound with compound (XI) in a solvent that does not adversely influence the reaction at room

temperature for about 0.5 to 24 hr. Where necessary, this reaction may be carried out in the presence of about 1 to 5 equivalents of a base.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like, acetonitrile, pyridine, ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (XIII) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

The amount of compound (XI) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

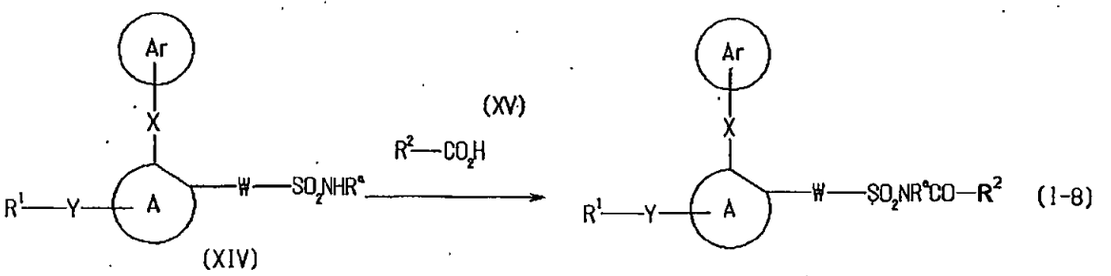
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

Compound (XIII) to be used as a starting material compound in the above-mentioned Method I can be produced according to a method known *per se*.

Compound (I-8) of the formula (I) wherein Z is $-SO_2NR^aCO-$ (R^a is as defined above) can be produced, for example, by the following Method J.

[Method J]



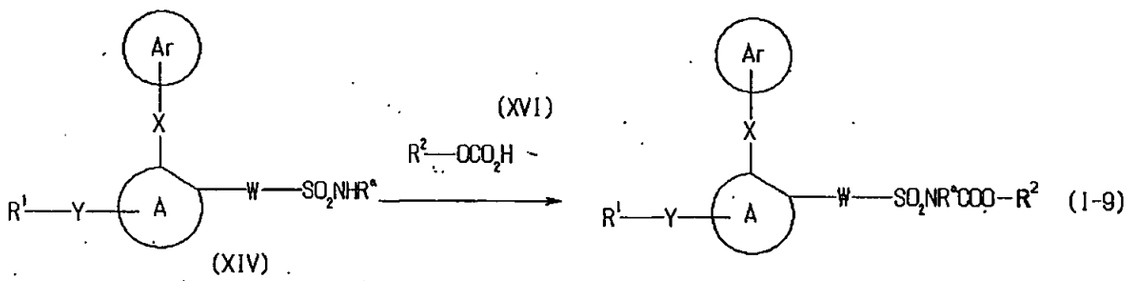
wherein the symbols in the formula are as defined above.

In the present method, compound (I-8) is produced by reacting compound (XIV) with compound (XV). This reaction is carried out in the same manner as in the amidation reaction described in the aforementioned Method A.

Compound (XV) to be used as a starting material compound in the above-mentioned Method J can be produced according to a method known *per se*.

Compound (I-9) of the formula (I) wherein Z is -SO_2NR^aCOO- (R^a is as defined above) can be produced, for example, by the following Method K.

[Method K]



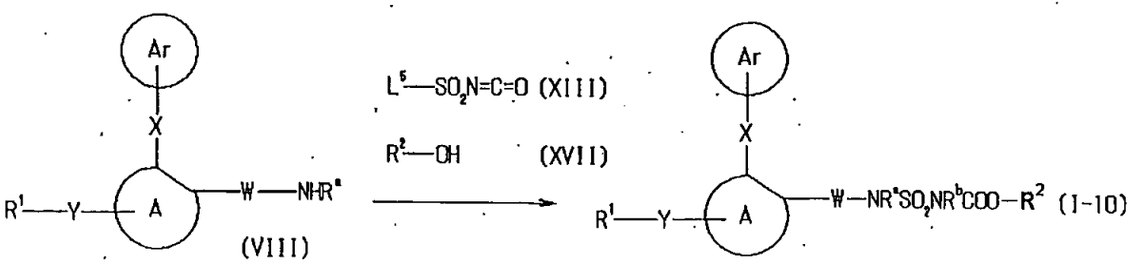
wherein the symbols in the formula are as defined above.

In the present method, compound (I-9) is produced by reacting compound (XIV) with compound (XVI). This reaction is carried out in the same manner as in the amidation reaction described in the aforementioned Method A.

Compound (XVI) to be used as a starting material compound in the above-mentioned Method K can be produced according to a method known *per se*.

Compound (I-10) of the formula (I) wherein Z is -$NR^aSO_2NR^bCOO$- (R^a and R^b are as defined above) can be produced, for example, by the following Method L.

[Method L]



wherein the symbols in the formula are as defined above.

In the present method, compound (I-10) is produced from compound (VIII). This reaction is carried out by a method known *per se*, for example, by reacting compound (VIII) with compound (XIII) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 5 hr, and reacting the obtained compound with compound (XVII) in a solvent that does not adversely influence the reaction at room temperature for about 0.5 to 24 hr. Where necessary, this reaction may be carried out in the presence of about 1 to 5 equivalents of a base.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like, acetonitrile, pyridine, ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (XIII) to be used is 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (VIII).

The amount of compound (XVII) to be used is 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (VIII).

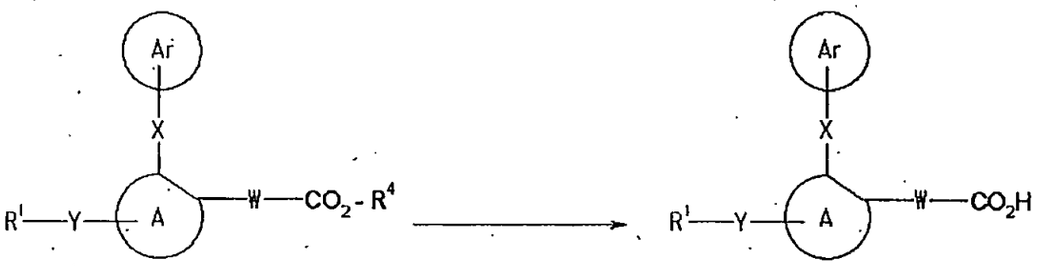
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

Compound (XVII) to be used as a starting material compound in the above-mentioned Method L can be produced according to a method known *per se*.

Compound (II) to be used as a starting material compound in the above-mentioned Method A and Method B can be produced, for example, by the following Method M.

[Method M]



wherein R^4 is an optionally substituted hydrocarbon group, and other symbols are as defined above.

Here, as the "optionally substituted hydrocarbon group" for the above-mentioned R^4, those exemplified as the aforementioned R^1 can be mentioned. R^4 is preferably a C_{1-6} alkyl group, more preferably methyl, ethyl and the like.

In the present method, compound (II) is produced by subjecting compound (XVIII) to a hydrolysis reaction. This reaction is carried out by a conventional method in the presence of an acid or base in a water-containing solvent.

As the acid, for example, inorganic acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic acids such as acetic acid and the like; and the like can be mentioned.

As the base, for example, alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide and the like;

alkali metal hydroxides such as potassium hydroxide, sodium hydroxide, lithium hydroxide and the like; and the like can be mentioned.

The amount of the acid or base to be used is generally an excess amount relative to compound (XVIII). The amount of the acid to be used is preferably about 2 to about 50 equivalents relative to compound (XVIII) and the amount of the base to be used is about 1.2 to about 5 equivalents relative to compound (XVIII).

As the water-containing solvent, for example, a mixed solvent of water with one or more kinds of solvents selected from alcohols such as methanol, ethanol and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; dimethyl sulfoxide, acetone and the like; and the like can be mentioned.

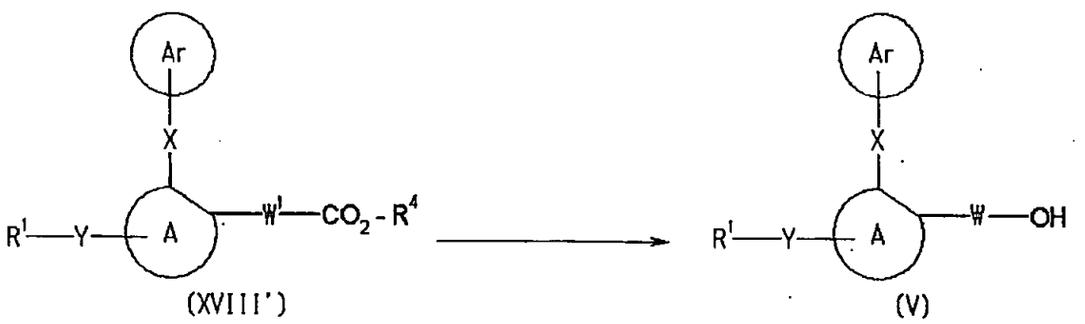
The reaction temperature is generally about -20°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.1 to about 20 hr.

Compound (XVIII) to be used as a starting material compound in the above-mentioned Method M can be produced, for example, by the below-mentioned Method P or a method analogous thereto.

Compound (V) to be used as a starting material compound in the above-mentioned Method C, Method D, Method E and Method I can be produced, for example, by the following Method N.

[Method N]



wherein W^1 is optionally substituted divalent hydrocarbon group having 1 to 19 carbon atoms, and other symbols are as defined above.

As the "optionally substituted divalent hydrocarbon group having 1 to 19 carbon atoms" for W^1, the aforementioned "optionally substituted divalent hydrocarbon group having 1 to 20 carbon atoms" for W, which contains 1 to 19 carbon atoms constituting the hydrocarbon group, can be used.

In the present method, compound (V) is produced by subjecting compound (XVIII') to a reduction reaction. This reaction is generally carried out in the presence of a reducing agent in a solvent that does not adversely influence the reaction.

As the reducing agent, for example, metal hydrogen compounds such as sodium bis(2-methoxyethoxy)aluminum hydride, diisobutylaluminum hydride and the like; metal hydrogen complex compounds such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, sodium aluminum hydride and the like; and the like can be mentioned.

The amount of the reducing agent to be used is generally 1 to 20 molar equivalents relative to compound (XVIII').

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

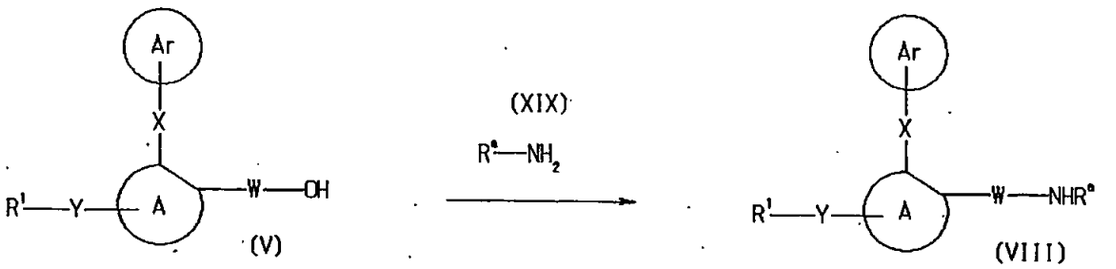
The reaction temperature is generally -70°C to 150°C, preferably -20°C to 100°C.

The reaction time is generally 0.1 to 100 hr, preferably 0.1 to 40 hr.

Compound (XVIII') to be used as a starting material compound in the above-mentioned Method N can be produced, for example, by the below-mentioned Method P or a method analogous thereto.

Compound (VIII) to be used as a starting material compound in the above-mentioned Method F, Method H and Method L can be produced, for example, by the following Method O.

[Method O]



wherein the symbols in the formula are as defined above.

In the present method, compound (VIII) is produced by subjecting compound (V) to an alkylation reaction. This reaction is carried out by a method known *per se*, by reacting a compound obtained by converting the hydroxy group of compound (V) to a leaving group (halogen atom or $-OSO_2R^3$) with compound (XIX) in the presence of a base in a solvent that does not adversely influence the reaction.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like,

acetonitrile, pyridine, ethyl acetate, water and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of compound (XIX) to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, relative to compound (V).

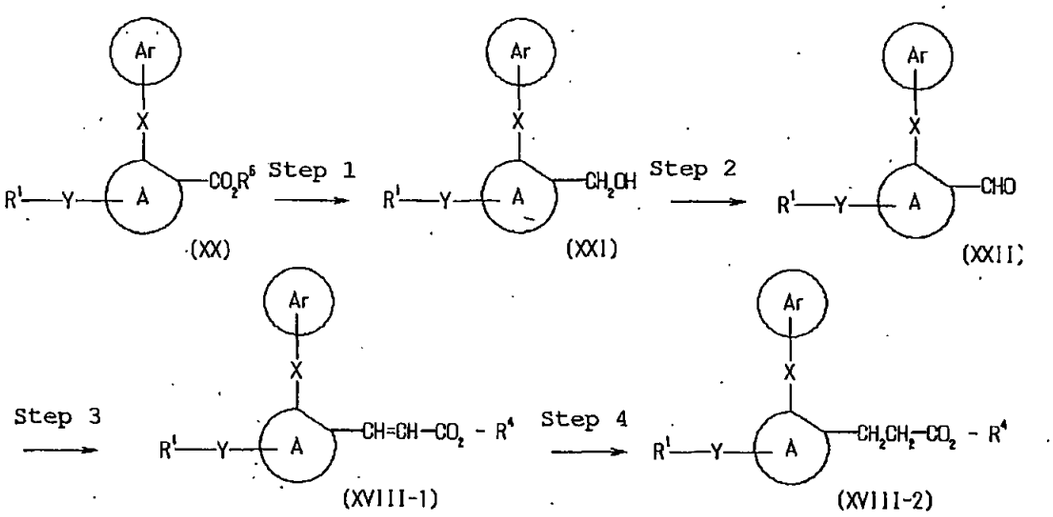
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 20 hr.

Compound (XIX) to be used as a starting material compound in the above-mentioned Method O can be produced according to a method known *per se*.

Of compounds (XVIII) to be used as starting material compounds in the above-mentioned Method M, compound (XVIII-1) and (XVIII-2) wherein W is -CH=CH- or $-CH_2CH_2-$ can be produced, for example, by the following Method P.

[Method P]



wherein R^5 is a C_{1-6} alkyl group, and other symbols are as defined above.

[step 1]

In this step, compound (XXI) is produced by subjecting compound (XX) to a reduction reaction. This reaction is carried out in the same manner as in the aforementioned Method N.

Compound (XX) can be produced, for example, by the method described in WO 01/38325 and the like, or a method analogous thereto.

[step 2]

In this step, compound (XXII) is produced by subjecting compound (XXI) to an oxidation reaction. This reaction is generally carried out in the presence of an oxidant in a solvent that does not adversely influence the reaction.

As the oxidant, for example, metal oxidants such as manganese dioxide, pyridinium chlorochlomate, pyridinium dichlorochlomate, ruthenium oxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of the metal oxidant to be used is generally 1 to 50 molar equivalents, preferably 1 to 10 molar equivalents, relative to compound (XXI).

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

Compound (XXII) can also be produced by dissolving compound (XXI) in dimethyl sulfoxide or a mixed solvent of dimethyl sulfoxide and halogenated hydrocarbon (e.g., chloroform, dichloromethane) at an appropriate ratio, adding a sulfur trioxide pyridine complex or oxalyl chloride, and reacting with an organic base (e.g., triethylamine, N-methylmorpholine).

The amount of the sulfur trioxide pyridine complex or oxalyl chloride to be used is 1 to 50 molar equivalents,

preferably 1 to 10 molar equivalents, relative to compound (XXI).

The amount of the organic base to be used is 1 to 50 molar equivalents, preferably 1 to 10 molar equivalents, relative to compound (XXI).

The reaction temperature is generally about -100°C to about 150°C, preferably about -70°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

[step 3]

In this step, compound (XVIII-1) is produced by subjecting compound (XXII) to a carbon addition reaction. This reaction is generally carried out using an organic phosphorus reagent in a solvent that does not adversely influence the reaction, and in the presence of a base.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the organic phosphorus reagent, for example, trimethyl phosphonoacetate, methyl diethylphosphonoacetate, triethyl phosphonoacetate, tert-butyl diethylphosphonoacetate and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like ; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide,

N-methylpyrrolidone and the like ; sulfoxides such as dimethyl sulfoxide and the like; alcohols such as methanol, ethanol, isopropanol, tert-butanol and the like; and the like can be mentioned. These solvents may be used as a mixture thereof at an appropriate ratio.

The amount of the base to be used is generally 1 to 50 molar equivalents, preferably 1 to 10 molar equivalents, relative to compound (XXII).

The amount of the organic phosphorus reagent to be used is generally 1 to 50 molar equivalents, preferably 1 to 10 molar equivalents, relative to compound (XXII).

The reaction temperature is generally about -100°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

[step 4]

In this step, compound (XVIII-2) is produced by subjecting compound (XVIII-1) to a hydrogenation reaction.

This reaction can be carried out, for example, in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium chloride, platinum oxide, platinum black, platinum-palladium, Raney-nickel, Raney-cobalt and the like and a hydrogen source, in a solvent that does not adversely influence the reaction.

The amount of the metal catalyst to be used is generally 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents, relative to compound (XVIII-1).

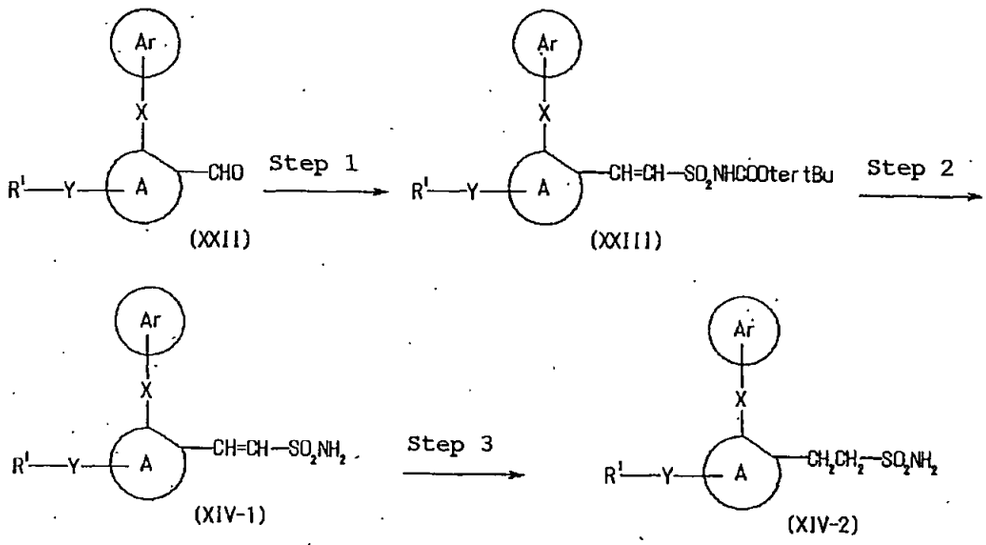
As the hydrogen source, for example, hydrogen gas, formic acid, formic acid amine salt, phosphinate, hydrazine and the like can be mentioned.

As the solvent that does not adversely influence the reaction, those exemplified in the aforementioned step 1 can be used.

The reaction temperature and the reaction time are the same as in the aforementioned step 1.

Of the compounds (XIV) to be used as a starting material compound in the above-mentioned Method J and Method K, compound (XIV-1) and (XIV-2) wherein W is -CH=CH- or $-CH_2CH_2-$ and R^a is a hydrogen atom can be produced, for example, by the following Method Q.

[Method Q]



(XXII) (XXIII) (XIV-1) (XIV-2)

wherein the symbols in the formula are as defined above.

[step 1]

In this step, compound (XXIII) is produced from compound (XXII). This reaction is carried out by a method known *per se*, for example, by the method described in Synthesis, page 2321 (2003), or a method analogous thereto.

[step 2]

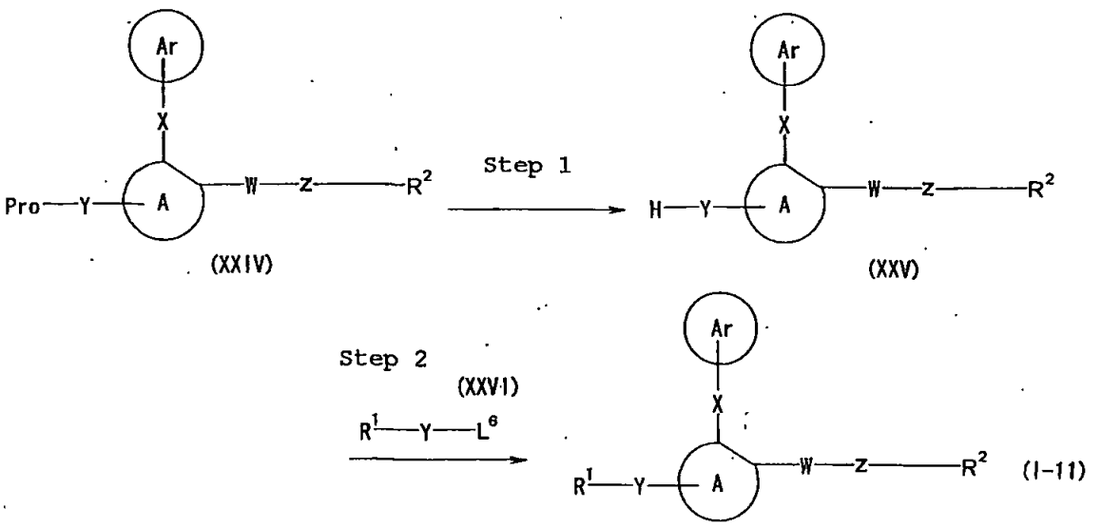
In this step, compound (XIV-1) is produced by subjecting compound (XXIII) to a deprotection reaction. This reaction is carried out by a method known *per se*.

[step 3]

In this step, compound (XIV-2) is produced by subjecting compound (XIV-1) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method P, step 4.

Compound (I-11) of the formula (I) wherein Y is an oxygen atom or a sulfur atom can be produced, for example, by the following Method R.

[Method R]



wherein Pro is a hydroxy-protecting group or a mercapto-protecting group, L^6 is a leaving group, and other symbols are as defined above.

Here, as the hydroxy-protecting group for Pro, for example, a C_{1-6} alkyl group, a C_{7-20} aralkyl group (e.g., benzyl, trityl), a formyl group, a C_{1-6} alkyl-carbonyl group, a benzoyl group, a C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), a 2-tetrahydropyranyl group, a tetrahydrofuranyl group or a substituted silyl group (e.g., a tri-C_{1-6} alkyl-silyl group such as trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl and tert-butyldiethylsilyl; tert-butyldiphenylsilyl) and the like, each optionally having substituent(s), can be mentioned. As used herein, as the substituent, for example, a halogen atom, a C_{1-6} alkyl group, a phenyl group, a C_{7-10} aralkyl group (e.g., benzyl), a C_{1-6} alkoxy group, a nitro group and the like are used. The number of the substituent is 1 to 4.

As the mercapto-protecting group for Pro, for example, a C_{1-6} alkyl group, a C_{7-20} aralkyl group (e.g., benzyl, trityl) and the like, each optionally having substituent(s), can be mentioned. As used herein, as the substituent, for example, a halogen atom, a C_{1-6} alkyl group, a phenyl group, a C_{7-10} aralkyl group (e.g., benzyl), a C_{1-6} alkoxy group, a C_{1-6} alkyl-carbonyl group, a nitro group and the like are used. The number of the

substituent is 1 to 4.

As the "leaving group" for L^6, those exemplified as the aforementioned L^1 and L^2 can be mentioned. Of those, a halogen atom or $-OSO_2R^3$ (R^3 is an alkyl group having 1 to 4 carbon atoms or an aryl group having 6 to 10 carbon atoms optionally substituted by an alkyl group having 1 to 4 carbon atoms) is preferable, and a chlorine atom and methanesulfonyloxy are particularly preferable.

[step 1]

In this step, compound (XXV) is produced by subjecting compound (XXIV) to a deprotection reaction. This reaction is carried out by a method known *per se*.

[step 2]

In this step, compound (I-11) is produced by reacting compound (XXV) with compound (XXVI). This reaction is carried out in the same manner as in the aforementioned Method G.

Compound (XXIV) to be used as a starting material compound in the above-mentioned Method R can be produced, for example, by any of the aforementioned Method A to Method L.

In addition, compound (XXVI) to be used as a starting material compound in the above-mentioned Method R can be produced according to a method known *per se*.

In each of the aforementioned reactions, when the starting material compound has an amino group, a carboxyl group, a hydroxy group, a carbonyl group or a mercapto group as a substituent, a protecting group generally used in the peptide chemistry and the like may be introduced into these groups, and the object compound can be obtained by eliminating the protecting group as necessary after the reaction.

The compound of the present invention obtained by each production method mentioned above can be isolated and purified by a known means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like. Each starting material compound used in each of the above-

mentioned production methods can be isolated and purified by a known means similar to those mentioned above. It is also possible to use such starting material compound as it is in a reaction mixture without isolation, as a starting material for the next step.

When compound (I) contains an optical isomer, a stereoisomer, a positional isomer or a rotational isomer, they are also encompassed in compound (I) and can be obtained as single products by synthesis techniques and separation techniques known *per se*. For example, when compound (I) contains an optical isomer, an optical isomer separated from the compound is also encompassed in compound (I).

The present invention is explained in detail in the following by referring to Experimental Example, Reference Examples, Examples and Formulation Examples, which are not to be construed as limitative.

Examples

In the following Reference Examples and Examples, % means wt% unless otherwise specified. In addition, room temperature means a temperature of 1-30°C unless otherwise specified.

Reference Example 1

To a solution of ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionate (5.21 g) in tetrahydrofuran (12 ml) and ethanol (12 ml) was added 1N aqueous sodium hydroxide solution (25 ml), and the mixture was stirred at 50°C for 30 min. After cooling to room temperature, 1N hydrochloric acid (25 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (4.15 g, yield: 85%) as white thin needles. melting point 116-117°C.

Reference Example 2

To a solution of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propionate (4.45 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added 1N aqueous sodium hydroxide solution (21 ml), and the mixture was stirred at 50°C for 40 min. After cooling to room temperature, 1N hydrochloric acid (21 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propionic acid (4.12 g, yield: 99%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (6 H, d, J = 6.0 Hz), 2.54 - 2.69 (2 H, m), 2.73 - 2.83 (2 H, m), 4.38 - 4.59 (1 H, m), 6.63 (1 H, d, J = 2.6 Hz), 6.77 (1 H, dd, J = 8.6, 2.5 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.3 Hz), 8.24 - 8.28 (1 H, m).

Reference Example 3

To a solution of 2-hydroxy-4-(methoxymethoxy)benzaldehyde (74.68 g) in N,N-dimethylformamide (450 ml) was added sodium hydride (60% in oil, 19.65 g) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, 2,3-dichloro-5-(trifluoromethyl)pyridine (60.0 ml) was added, and the mixture was stirred at room temperature for 1 hr and at 50°C for 1 hr. After cooling the reaction mixture to ice temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:2, v/v) to give a pale-yellow solid.

Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-

(methoxymethoxy)benzaldehyde (79.00 g, yield: 53%) as white crystals. melting point 93.9-94.0°C.

Reference Example 4

To a solution of ethyl diethylphosphonoacetate (2.76 g) in tetrahydrofuran (10 ml) was added sodium hydride (60% in oil, 482 mg) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)benzaldehyde (3.90 g) in N,N-dimethylformamide (10 ml) was added dropwise, and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 35:65, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]acrylate (4.66 g, yield: quant.) as a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave white feather crystals. melting point 73.5-74.5°C.

Reference Example 5

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]acrylate (52.85 g) in acetone (500 ml) was added 1N hydrochloric acid (250 ml), and the mixture was stirred with heating under reflux for 5 hr. After cooling to room temperature, a 1N aqueous sodium hydroxide solution (250 ml) was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed twice with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]acrylate

(44.52 g, yield: quant.) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 123.5-124.0°C.

Reference Example 6

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]acrylate (41.68 g) in tetrahydrofuran (1000 ml) were added tributylphosphine (49.0 ml), 2-methoxyethanol (13.0 ml) and 1,1'-azodicarbonyldipiperidine (41.01 g), and the mixture was stirred at 50°C for 20 min. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylate (28.67 g, yield: 60%) as white feather crystals. melting point 78.2-78.5°C.

Reference Example 7

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylate (2.39 g) in tetrahydrofuran (5.0 ml) and ethanol (5.0 ml) was added a 1N aqueous sodium hydroxide solution (18.0 ml), and the mixture was stirred at 50°C for 1 hr. After cooling to room temperature, 1N hydrochloric acid (18.0 ml) was added to the reaction mixture, and the mixture was diluted with toluene and concentrated. The residue was dissolved in ethyl acetate, and the organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (1.77 g, yield: 79%) as white feather crystals. melting point 156.5-157.5°C.

Reference Example 8

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]acrylate (41.53 g) in N,N-dimethylformamide (10 ml) were added 2-propyl iodide (0.65 ml) and potassium carbonate (712 mg), and the mixture was stirred at 50°C for 1 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:3, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]acrylate (1.63 g, yield: 96%) as a white solid. Recrystallization from ethyl acetate-hexane gave white feather crystals. melting point 84.5-85.0°C.

Reference Example 9

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]acrylate (1.53 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (8.0 ml), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid (8.0 ml) was added to the reaction mixture, and the mixture was diluted with toluene and concentrated. The residue was dissolved in ethyl acetate, and the organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]acrylic acid (0.91 g, yield: 63%) as a white powder. melting point 138.0-139.5°C.

Reference Example 10

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]propan-1-ol (4.94 g) in ethyl acetate (100 ml) were added triethylamine (3.50 ml) and methanesulfonyl chloride (1.40 ml), and the mixture was stirred at room temperature for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow oil.

To a solution of the obtained oil in N,N-dimethylformamide (50 ml) was added potassium phthalimide (2.46 g), and the mixture was stirred at 80°C for 3 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. The solid was washed with diisopropyl ether to give 2-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (6.39 g, yield: 98%). Recrystallization from ethyl acetate-hexane gave white crystals. melting point 101-103°C.

Reference Example 11

To a solution of 2-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (6.12 g) in methanol (100 ml) was added hydrazine monohydrate (4.02 g), and the mixture was stirred at 50°C for 2 hr. The reaction mixture was concentrated, the residue was washed with diethyl ether, and the filtrate was concentrated. The obtained residue was dissolved in diethyl ether, and the organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (2.51 g, yield: 54%) as a

dark-brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.51 - 1.95 (4 H, m), 2.40 - 2.55 (2 H, m), 2.68 (2 H, t, J = 7.0 Hz), 3.44 (3 H, s), 3.65 - 3.80 (2 H, m), 4.05 - 4.11(2 H, m), 6.67 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.4, 2.5 Hz), 7.21 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.26 (1 H, d, J = 0.9 Hz).

Reference Example 12

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylate (3.73 g) in tetrahydrofuran (100 ml) was added a 1.5 M solution (19.0 ml) of diisobutylaluminum hydride in toluene under ice-cooling, and the mixture was stirred for 5 min. A saturated aqueous ammonium chloride solution (5.40 ml) was added to the reaction mixture, and the precipitated solid was filtered off and the filtrate was concentrated to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propen-1-ol (3.26 g, yield: 97%) as a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 119-121°C.

Reference Example 13

To a solution of 2,4-dihydroxyacetophenone (25.12 g) in tetrahydrofuran (1000 ml) were added triphenylphosphine (70.91 g), 2-methoxyethanol (20.0 ml) and a diethyl azodicarboxylate 40% toluene solution (120 ml) under ice-cooling, and the mixture was stirred at room temperature for 2.5 hr. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give 1-[2-hydroxy-4-(2-methoxyethoxy)phenyl]ethanone (17.96 g, yield: 52%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.56 (3 H, s), 3.45 (3 H, s), 3.67 - 3.82 (2 H, m), 4.09 - 4.19 (2 H, m), 6.43 (1 H, d, J = 2.4 Hz), 6.49 (1 H, dd, J = 8.9, 2.4 Hz), 7.63 (1 H, d, J = 9.0 Hz), 12.73 (1 H, s).

Reference Example 14

To a solution of 1-[2-hydroxy-4-(2-methoxyethoxy)phenyl]ethanone (5.08 g) in N,N-dimethylformamide (50 ml) were added potassium carbonate (4.71 g) and benzyl bromide (3.50 ml), and the mixture was stirred at room temperature for 3 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give 1-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]ethanone (7.00 g, yield: 97%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.55 (3 H, s), 3.45 (3 H, s), 3.65 - 3.79 (2 H, m), 4.09 - 4.20 (2 H, m), 5.13 (2 H, s), 6.45 - 6.70 (2 H, m), 7.32 - 7.51 (5 H, m), 7.84 (1 H, d, J = 8.7 Hz).

Reference Example 15

To a solution of ethyl diethylphosphonoacetate (7.34 g) in ethanol (45 ml) was added sodium ethoxide (1.93 g) under ice-cooling, and the mixture was stirred at room temperature for 20 min. To the reaction mixture was added a solution of 1-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]ethanone (7.00 g) in ethanol (45 ml), and the mixture was stirred with heating under reflux for 20 hr. After cooling to room temperature, a saturated aqueous ammonium chloride solution was added, and the mixture was diluted with toluene and concentrated. The residue was dissolved in ethyl acetate, and the organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 35:65, v/v) to give ethyl (2E)-3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]-2-butenoate (Reference Example 15a: 6.17 g, yield: 72%) as a colorless

oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.29 (3 H, t, J = 7.1 Hz), 2.50 (3 H, d, J = 1.3 Hz), 3.45 (3 H, s), 3.70 - 3.78 (2 H, m), 4.06 - 4.13 (2 H, m), 4.19 (2 H, q, J = 7.2 Hz), 5.05 (2 H, s), 5.93 (1 H, d, J = 1.3 Hz), 6.48 (1 H, dd, J = 8.4, 2.4 Hz), 6.59 (1 H, d, J = 2.3 Hz), 7.11 (1 H, d, J = 8.3 Hz), 7.28 - 7.46 (5 H, m).

Then, ethyl (2Z)-3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]-2-butenoate (Reference Example 15b: 1.90 g, yield: 22%) was obtained as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.06 (3 H, t, J = 7.1 Hz), 2.15 (3 H, d, J = 1.3 Hz), 3.44 (3 H, s), 3.66 - 3.79 (2 H, m), 3.96 (2 H, q, J = 7.0 Hz), 4.06 - 4.14 (2 H, m), 5.03 (2 H, s), 5.93 (1 H, d, J = 1.5 Hz), 6.50 (1 H, dd, J = 8.4, 2.4 Hz), 6.58 (1 H, d, J = 2.3 Hz), 6.96 (1 H, d, J = 8.3 Hz), 7.29 - 7.40 (5 H, m).

Reference Example 16

To a solution of ethyl (2E)-3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]-2-butenoate (6.17 g) in tetrahydrofuran (20 ml) and ethanol (20 ml) was added 10% palladium-carbon (1.91 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated and the filtrate was concentrated to give ethyl 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]butanoate (4.36 g, yield: 93%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.19 (3 H, t, J = 7.2 Hz), 1.30 (3 H, d, J = 7.2 Hz), 2.49 - 2.70 (2 H, m), 3.44 (3 H, s), 3.45 - 3.56 (1 H, m), 3.70 - 3.74 (2 H, m), 4.00 - 4.16 (4 H, m), 6.45 - 6.49 (1 H, m), 6.50 - 6.59 (1 H, m), 6.93 (1 H, s), 7.04 (1 H, d, J = 8.5 Hz).

Reference Example 17

To a solution of ethyl 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]butanoate (5.50 g) in N,N-dimethylformamide (40 ml) was added sodium hydride (60% in oil, 932 mg) under ice-cooling, and the mixture was

subsequently stirred for 30 min. Then, 2,3-dichloro-5-(trifluoromethyl)pyridine (3.0 ml) was added, and the mixture was stirred at room temperature for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 35:65, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoate (7.80 g, yield: 87%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.16 (3 H, t, J = 7.2 Hz), 1.22 (3 H, d, J = 7.0 Hz), 2.39 - 2.50 (1 H, m), 2.56 - 2.70 (1 H, m), 3.23 - 3.38 (1 H, m), 3.43 (3 H, s), 3.65 - 3.79 (2 H, m), 3.96 - 4.19 (4 H, m), 6.66 (1 H, d, J = 2.6 Hz), 6.85 (1 H, dd, J = 8.7, 2.6 Hz), 7.18 - 7.29 (1 H, m), 7.98 (1 H, d, J = 2.1 Hz), 8.25 (1 H, d, J = 1.1 Hz).

Reference Example 18

To a solution of ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoate (7.80 g) in tetrahydrofuran (45 ml) was added a 1.0 M solution (80.0 ml) of diisobutylaluminum hydride in hexane under ice-cooling, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution (15.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. The precipitated solid was filtered off and the filtrate was concentrated to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butan-1-ol (7.46 g, yield: quant.) as an orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.20 (3 H, d, J = 7.0 Hz), 1.62 (1 H, t, J = 6.0 Hz), 1.75 - 1.87 (2 H, m), 2.90 - 3.05 (1 H, m), 3.43 (3 H, s), 3.50 (2 H, q, J = 5.9 Hz), 3.68 - 3.77 (2 H,

m), 3.90 - 4.24 (2 H, m), 6.61 (1 H, d, J = 2.6 Hz), 6.89 (1 H, dd, J = 8.7, 2.6 Hz), 7.09 - 7.34 (1 H, m), 7.99 (1 H, d, J = 1.7 Hz), 8.25 (1 H, dd, J = 2.2, 1.0 Hz).

Reference Example 19

To a solution of triethyl 2-phosphonopropionate (7.93 g) in tetrahydrofuran (30 ml) was added sodium hydride (60% in oil, 1.31 g) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)benzaldehyde (10.01 g) in N,N-dimethylformamide (30 ml) was added dropwise, and the mixture was stirred at room temperature for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:2, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]-2-methyl acrylate (13.71 g, yield: quant.) as a pale-yellow oil (E/Z = 10:1.5).

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.25 (3 H, t, J = 7.2 Hz), 2.01 (3 H, d, J = 1.5 Hz), 3.50 (3 H, s), 4.17 (2 H, q, J = 7.2 Hz), 5.20 (2 H, s), 6.92 (1 H, d, J = 2.4 Hz), 7.01 (1 H, dd, J = 8.7, 2.4 Hz), 7.38 (1 H, d, J = 8.5 Hz), 7.49 (1 H, s), 7.96 (1 H, d, J = 1.9 Hz), 8.23 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Example 20

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]-2-methyl acrylate (13.71 g) in acetone (150 ml) was added 1N hydrochloric acid (60 ml), and the mixture was stirred overnight at 50°C. After cooling to room temperature, a 1N aqueous sodium hydroxide solution (60 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated

brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]-2-methyl acrylate (10.13 g, yield: 91%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 101.5-102.0°C.

Reference Example 21

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]-2-methyl acrylate (4.96 g) in tetrahydrofuran (100 ml) were added tributylphosphine (6.00 ml), 2-methoxyethanol (1.50 ml) and 1,1'-azodicarbonyldipiperidine (4.51 g), and the mixture was stirred at 50°C for 30 min. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl acrylate (5.38 g, yield: 95%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.23 - 1.29 (3 H, m), 2.02 (3 H, d, J = 1.5 Hz), 3.45 (3 H, s), 3.73 - 3.80 (2 H, m), 4.06 - 4.23 (4 H, m), 6.78 (1 H, d, J = 2.6 Hz), 6.91 (1 H, dd, J = 8.7, 2.4 Hz), 7.39 (1 H, d, J = 8.7 Hz), 7.50 (1 H, s), 7.96 (1 H, d, J = 2.1 Hz), 8.22 (1 H, d, J = 1.1 Hz).

Reference Example 22

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl acrylate (1.76 g) in tetrahydrofuran (40 ml) was added 10% palladium-carbon (1.91 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated. A 1.0 M solution (16.0 ml) of diisobutylaluminum hydride in hexane was added to the filtrate under ice-cooling, and the mixture was stirred at

room temperature. After 1 hr, a 1.0 M solution (14.0 ml) of diisobutylaluminum hydride in hexane was added at room temperature, and the mixture was stirred for 1 hr. A saturated aqueous ammonium chloride solution (5.70 ml) was added to the reaction mixture under ice-cooling, and the mixture was stirred for 1 hr. The precipitated solid was filtered off and the filtrate was concentrated to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylpropan-1-ol (1.41 g, yield: 88%) as a white solid. Recrystallization from ethyl acetate-hexane gave white feather crystals. melting point 84-86°C.

Reference Example 23

To a solution of ethyl 3-(2-hydroxy-4-isopropoxyphenyl)propionate (10.0 g) in N,N-dimethylformamide (150 ml) was added sodium hydride (60% in oil, 1.92 g) at room temperature, and the mixture was stirred for 30 min. 2,4-Dichlorobenzyl chloride (6.7 ml) was added, and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated.

The obtained residue was dissolved in tetrahydrofuran (300 ml), lithium aluminum hydride (1.52 g) was added at room temperature, and the mixture was stirred for 30 min. Sodium sulfate 10 hydrate (12.9 g) was added to the reaction mixture, and the resulting solid was filtered off and the filtrate was concentrated. Recrystallization of the residual solid from ethyl acetate-hexane gave 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}propan-1-ol (11.2 g, yield: 76%) as colorless needles. melting point 75.5-76.5°C.

Reference Example 24

To a solution of 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}propan-1-ol (2.54 g) in dichloromethane (20 ml) was added Dess-Martin reagent (3.21 g) under ice-cooling, and the mixture was stirred at room temperature for 30 min. A

saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}propanal (2.88 g, yield: quant.) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.22 - 1.39 (6 H, m), 2.67 - 2.83 (2 H, m), 2.94 (2 H, t, J = 7.4 Hz), 4.33 - 4.60 (1 H, m), 5.08 (2 H, s), 6.41 - 6.54 (1 H, m), 7.05 (1 H, d, J = 8.7 Hz), 7.29 (1 H, dd, J = 8.3, 2.1 Hz), 7.39 - 7.50 (1 H, m), 7.65 - 7.78 (1 H, m), 7.84 - 8.07 (2 H, m), 8.27 (1 H, dd, J = 7.6, 1.2 Hz), 9.79 (1 H, t, J = 1.7 Hz).

Reference Example 25

To a solution of 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}propanal (2.88 g) in tetrahydrofuran (12 ml), tert-butanol (12 ml) and water (12 ml), sodium dihydrogen phosphate (0.91 g), sodium chlorite (1.90 g) and 2-methyl-2-butene (4.0 ml) were added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. Recrystallization of the obtained residue from ethyl acetate-hexane and washing with diisopropyl ether gave 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}propionic acid (1.03 g, yield: 39%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.30 - 1.34 (6 H, m), 2.61 - 2.71 (2 H, m), 2.95 (2 H, t, J = 7.7 Hz), 4.41 - 4.56 (1 H, m), 5.06 - 5.13 (2 H, m), 6.40 - 6.49 (2 H, m), 7.08 (1 H, d, J = 8.5 Hz), 7.29 (1 H, dd, J = 8.4, 2.2 Hz), 7.42 (1 H, d, J = 2.1 Hz), 7.50 (1 H, d, J = 8.3 Hz).

Reference Example 26

To a solution of ethyl 3-[2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propionate (27.52 g) in tetrahydrofuran (320 ml) was added concentrated hydrochloric acid (10.0 ml), and the mixture was stirred at 50°C for 45 min. After cooling to room temperature, a 1N aqueous sodium hydroxide solution (120 ml) was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:4, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]propionate (20.54 g, yield: 83%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.09 - 1.38 (3 H, m), 2.44 - 2.68 (2 H, m), 2.68 - 2.85 (2 H, m), 3.97 - 4.25 (2 H, m), 6.61 (1 H, d, J = 2.2 Hz), 6.65 - 6.77 (1 H, m), 7.18 (1 H, d, J = 8.1 Hz), 7.98 (1 H, d, J = 2.2 Hz), 8.26 (1 H, s).

Reference Example 27

To a solution of ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]propionate (0.68 g) in N,N-dimethylformamide (15 ml) were added potassium carbonate (321.5 mg) and 2-chloro-N,N-diethylacetamide (0.31 g), and the mixture was stirred at room temperature for 2 hr, at 50°C for 30 min, and at 80°C for 1 hr. 2-Chloro-N,N-diethylacetamide (0.30 g) was added, and the mixture was further stirred for 30 min. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:2, v/v) to give ethyl 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propionate (1.39 g, yield: quant.) as a white

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solid. Recrystallization from ethyl acetate-hexane gave white cotton crystals. melting point 88.5-89.0°C.

Reference Example 28

To a solution of 1-bromo-3-methoxypropane (19.50 g) in N,N-dimethylformamide (200 ml) was added potassium thioacetate (15.15 g), and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a yellow oil.

To a solution of the obtained oil in diethyl ether (200 ml) was added 1N aqueous sodium hydroxide solution (250 ml) under ice-cooling, and the mixture was stirred under ice-cooling. After 1 hr, a 12N aqueous sodium hydroxide solution (20 ml) and methanol (50 ml) were added, and the mixture was stirred at room temperature for 20 min. Concentrated hydrochloric acid (45 ml) was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated.

Into a solution of the obtained residue in acetic acid (200 ml) and water (200 ml) was blown gaseous chlorine over 2 hr so that the temperature in the system would not rise to 15°C or above. Gaseous nitrogen was blown in at room temperature for 1 hr, the reaction mixture was added dropwise to an ice-cooled saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with diethyl ether. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution, a 10% aqueous sodium thiosulfate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow oil.

A solution of the obtained oil in tetrahydrofuran (10 ml) was added dropwise to a solution of 28% aqueous ammonia (50 ml) and tetrahydrofuran (50 ml) under ice-cooling, and the

mixture was subsequently stirred for 30 min. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give an orange oil. The obtained oil was dissolved in a suspension of activated carbon in ethyl acetate, and the mixture was stirred at room temperature for 1 hr. The mixture was filtrated and concentrated to give 3-methoxypropane-1-sulfonamide (0.88 g, yield: 5%) as an orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.86 - 2.25 (2 H, m), 3.19 - 3.28 (2 H, m), 3.35 (3 H, s), 3.53 (2 H, t, J = 5.8 Hz), 4.71 (2 H, s).

Reference Example 29

To a solution of ethyl (2E)-3-[2-(benzyloxy)-4-hydroxyphenyl]acrylate (2.01 g) in tetrahydrofuran (100 ml) were added triphenylphosphine (2.65 g), 1-(2-hydroxyethyl)-2-pyrrolidone (0.80 ml) and a diethyl azodicarboxylate 40% toluene solution (5.50 ml) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:3 to ethyl acetate alone, v/v), then ethyl acetate-methanol (ethyl acetate alone to 9:1, v/v) to give ethyl (2E)-3-{2-(benzyloxy)-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}acrylate (4.01 g, yield: quant.) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 94-97°C.

Reference Example 30

To a solution of (2E)-3-{2-(benzyloxy)-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}ethyl acrylate (3.81 g) in tetrahydrofuran (25 ml) and ethanol (25 ml) was added 10% palladium-carbon (1.00 g), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtrated and the filtrate was concentrated to give ethyl 3-{2-hydroxy-4-[2-(2-oxopyrrolidin-

1-yl)ethoxy]phenyl}propionate (3.05 g, yield: quant.) as a pale-brown solid. Recrystallization from ethyl acetate-diisopropyl ether gave a white powder. melting point 112-115°C.

Reference Example 31

To a solution of ethyl 3-{2-hydroxy-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}propionate (2.90 g) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 464 mg) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, 2,3-dichloro-5-(trifluoromethyl)pyridine (1.50 ml) was added, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1 to ethyl acetate alone, v/v) to give an orange oil.

To a solution of the obtained oil in tetrahydrofuran (15 ml) and ethanol (15 ml) was added a 1N aqueous sodium hydroxide solution (16.0 ml), and the mixture was stirred overnight at room temperature. 1N Aqueous sodium hydroxide solution (15.0 ml) was added and, after 1 hr, a 1N aqueous sodium hydroxide solution (10.0 ml) was further added, and the mixture was stirred for 1 hr. 1N Hydrochloric acid (41.0 ml) was added to the reaction mixture, and the mixture was concentrated. The residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 to ethyl acetate alone, v/v), then ethyl acetate-methanol (ethyl acetate alone to 9:1, v/v), to give 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}propionic

acid (0.85 g, 27%) as a white solid. Recrystallization from ethyl acetate-hexane gave a white powder. melting point 145.0-145.5°C.

Reference Example 32

To a solution of ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl]propionate (3.26 g) in dichloromethane (40 ml) were added 2,6-lutidine (2.0 ml) and triisopropylsilyl trifluoromethanesulfonate (2.50 ml) under ice-cooling, and the mixture was stirred for 30 min. Under ice-cooling, 2,6-lutidine (2.0 ml) and triisopropylsilyl trifluoromethanesulfonate (2.50 ml) were further added, and the mixture was stirred for 15 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 35:65, v/v) to give a yellow oil.

To a solution of the obtained oil in tetrahydrofuran (40 ml) was added a 1.5 M solution (20.0 ml) of diisobutylaluminum hydride in toluene under ice-cooling, and the mixture was stirred for 15 min. A saturated aqueous ammonium chloride solution (5.80 ml) was added to the reaction mixture, and the precipitated solid was filtered off and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v) to give a yellow oil.

To a solution of the obtained oil in N,N-dimethylformamide (10 ml) was added N,N'-carbonyldiimidazole (345 mg), and the mixture was stirred at 40°C for 1 hr. Cyclopropylmethylamine (834 mg) was added to the reaction mixture, and the mixture was stirred at 50°C for 5 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl

acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give an orange oil.

To a solution of the obtained oil in tetrahydrofuran (4 ml) was added tetrabutylammoniumfluoride 1.0 M tetrahydrofuran solution (4.0 ml), and the mixture was stirred at room temperature for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propyl (cyclopropylmethyl)carbamate (749 mg, yield: 39%) as a pale-orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.11 - 0.25 (2 H, m), 0.41 - 0.56 (2 H, m), 0.72 - 1.19 (1 H, m), 1.78 - 1.95 (2 H, m), 2.50 (2 H, t, J = 7.5 Hz), 2.95 - 3.07 (2 H, m), 4.02 (2 H, t, J = 6.1 Hz), 4.71 (1 H, s), 6.58 - 6.63 (1 H, m), 6.67 - 6.79 (1 H, m), 7.12 - 7.19 (1 H, m), 7.98 (1 H, d, J = 2.3 Hz), 8.27 (1 H, dd, J = 2.0, 1.0 Hz).

Reference Example 33

To a solution of 2,4-dihydroxybenzaldehyde (25.29 g) in tetrahydrofuran (1000 ml) were added triphenylphosphine (70.34 g), 2-methoxyethanol (20.0 ml) and a diethyl azodicarboxylate 40% toluene solution (120 ml) under ice-cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-hydroxy-4-(2-methoxyethoxy)benzaldehyde (12.65 g, yield: 35%) as white fine needles. melting point 64.5-65.5°C.

Reference Example 34

To a solution of 2-hydroxy-4-(2-methoxyethoxy)benzaldehyde (12.86 g) in N,N-dimethylformamide (100 ml) was added sodium hydride (60% in oil, 3.24 g) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, 2,3-dichloro-5-(trifluoromethyl)pyridine (12.0 ml) was added, and the mixture was stirred at room temperature for 3 hr and at 50°C for 30 min. After cooling the reaction mixture to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v). Activated carbon was suspended in the eluted fraction, and the suspension was stirred for 1 hr, filtrated and concentrated to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzaldehyde (14.66 g, yield: 60%) as a pale-yellow powder. Recrystallization from ethyl acetate-hexane gave a white prism, melting point 80.5-81.0°C.

Reference Example 35

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzaldehyde (13.04 g) in tetrahydrofuran (50 ml) and methanol (30 ml) was added sodium borohydride (3.99 g) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. Sodium borohydride (1.21 g) was further added, and the mixture was stirred for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:4 - 1:1, v/v) and then to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1 to

ethyl acetate alone, v/v) to give [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (2.51 g, yield: 19%) as a white solid. Recrystallization from ethyl acetate-hexane gave white feather crystals. melting point 85.0-85.5°C.

Reference Example 36

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxymethoxy)benzaldehyde (26.42 g) in tetrahydrofuran (500 ml) was added concentrated hydrochloric acid (50.0 ml), and the mixture was stirred at room temperature for 17 hr. A 1N aqueous sodium hydroxide solution (600 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:2, v/v) to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxybenzaldehyde (22.63 g, yield: 98%) as a pale-pink solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 129°C (dec.).

Reference Example 37

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxybenzaldehyde (3.12 g) in N,N-dimethylformamide (20 ml) was added potassium carbonate (2.25 g) and 1-iodobutane (1.50 ml), and the mixture was stirred at 50°C for 1 hr. After cooling the reaction mixture to room temperature, the mixture was extracted with a saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a pale-yellow oil.

To a solution of the obtained oil in tetrahydrofuran (15

ml) and methanol (15 ml) was added sodium borohydride (895 mg) under ice-cooling, and the mixture was stirred for 30 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The concentrate was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give (4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)methanol (2.76 g, yield: 75%) as a white solid. Recrystallization from ethyl acetate-hexane gave white fine needles. melting point 77.8-79.2°C.

Reference Example 38

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxybenzaldehyde (3.09 g) in N,N-dimethylformamide (20 ml) was added potassium carbonate (2.08 g) and 2-iodopropane (1.50 ml), and the mixture was stirred at 50°C for 1.5 hr. After cooling the reaction mixture to room temperature, the mixture was extracted with a saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give a pale-yellow oil.

To a solution of the obtained oil in tetrahydrofuran (15 ml) and methanol (15 ml) was added sodium borohydride (912 mg) under ice-cooling, and the mixture was stirred for 30 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The concentrate was subjected to basic silica gel column chromatography, and eluted with ethyl

acetate-hexane (1:9 - 1:1, v/v) to give (2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)methanol (2.48 g, yield: 71%) as a white solid. Recrystallization from ethyl acetate-hexane gave a white powder. melting point 63.0-64.0°C.

Reference Example 39

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxybenzaldehyde (3.09 g) in tetrahydrofuran (50 ml) were added pyridine (5.0 ml) and 1-propanesulfonyl chloride (1.60 ml), and the mixture was stirred at room temperature for 30 min. Then, triethylamine (5.0 ml), 1-propanesulfonyl chloride (1.60 ml) and ethyl acetate (50 ml) were added, and the mixture was stirred at room temperature for 2 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a yellow oil.

To a solution of the obtained oil in methanol (30 ml) was added sodium borohydride (385.1 mg) under ice-cooling, and the mixture was stirred for 20 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The concentrate was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:2, v/v) to give 3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(hydroxymethyl)phenyl propane-1-sulfonate (2.44 g, yield: 59%) as a white solid. Recrystallization from ethyl acetate-hexane gave white feather crystals. melting point 68.5-69.5°C.

Reference Example 40

A solution of sulfamide (811 mg) and N-methylhexylamine (1.00 ml) in 1,2-dimethoxyethane (25 ml) was stirred overnight with heating under reflux. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give N-hexyl-N-methylsulfamide (0.67 g, yield: 52%) as a pale-yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.80 - 0.96 (3 H, m), 1.10 - 1.43 (6 H, m), 1.46 - 1.62 (2 H, m), 2.80 (3 H, s), 2.98 - 3.17 (2 H, m), 4.56 (2 H, s).

Reference Example 41

To a solution of 2-hydroxy-4-(2-methoxyethoxy)benzaldehyde (9.30 g) in N,N-dimethylformamide (100 ml) were added potassium carbonate (6.91 g) and benzyl bromide (7.0 ml), and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-(benzyloxy)-4-(2-methoxyethoxy)benzaldehyde (10.71 g, yield: 79%) as white crystals. melting point 67.5-68.0°C.

Reference Example 42

To a solution of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphoniumbromide (6.96 g) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 628 mg) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, a solution of 2-(benzyloxy)-4-(2-methoxyethoxy)benzaldehyde (3.12 g) in N,N-dimethylformamide (30 ml) was added dropwise, and the mixture

was stirred at room temperature for 1 hr and at 80°C for 5 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a colorless oil.

To a solution of the obtained oil in ethanol (50 ml) was added 10% palladium-carbon (3.16 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give 2-[3-(1,3-dioxolan-2-yl)propyl]-5-(2-methoxyethoxy)phenol (0.93 g, yield: 30%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.64 - 1.87 (4 H, m), 2.61 (2 H, t, J = 6.8 Hz), 3.44 (3 H, s), 3.64 - 3.77 (2 H, m), 3.84 - 3.94 (2 H, m), 3.94 - 4.26 (4 H, m), 4.91 (1 H, t, J = 4.3 Hz), 6.22 (1 H, s), 6.33 - 6.62 (2 H, m), 6.96 (1 H, d, J = 8.1 Hz).

Reference Example 43

To a solution of 2-[3-(1,3-dioxolan-2-yl)propyl]-5-(2-methoxyethoxy)phenol (0.93 g) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 155 mg) under ice-cooling, and the mixture was subsequently stirred for 30 min. Then, 2,3-dichloro-5-(trifluoromethyl)pyridine (0.50 ml) was added, and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give 3-chloro-2-[2-[3-(1,3-dioxolan-2-yl)propyl]-

5-(2-methoxyethoxy)phenoxy]-5-(trifluoromethyl)pyridine (1.33 g, yield: 87%) as a white solid. Recrystallization from ethyl acetate-hexane gave a white powder. melting point 92.0-92.5°C.

Reference Example 44

A solution of 3-chloro-2-[2-[3-(1,3-dioxolan-2-yl)propyl]-5-(2-methoxyethoxy)phenoxy]-5-(trifluoromethyl)pyridine (1.08 g) in a 80% aqueous acetic acid solution (15 ml) was stirred at 50°C for 4 hr and at 80°C for 3 hr. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a pale-yellow oil.

To a solution of the obtained oil in tert-butanol (10 ml) and water (2.5 ml) were added sodium dihydrogen phosphate (313 mg), sodium chlorite (645 mg) and 2-methyl-2-butene (4.5 ml) at room temperature, and the mixture was stirred at room temperature for 30 min. A 10% aqueous sodium hydrogen sulfite solution and 1N hydrochloric acid were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. Recrystallization of the obtained residue from ethyl acetate-hexane gave 4-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoic acid (612 mg, yield: 60%) as white fine needles. melting point 119.0-119.5°C.

Reference Example 45

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butan-1-ol (2.63 g) in dichloromethane (30 ml) was added a Dess-Martin reagent (3.46 g) under ice-cooling, and the mixture was stirred at room temperature for 10 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated.

The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give a pale-yellow oil.

To a solution of the obtained oil in tetrahydrofuran (30 ml), tert-butanol (24 ml) and water (6 ml) were added sodium dihydrogen phosphate (803 mg), sodium chlorite (601 mg) and 2-methyl-2-butene (6.5 ml) at room temperature, and the mixture was stirred at room temperature for 20 min. A 10% aqueous sodium hydrogen sulfite solution and 1N hydrochloric acid were added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 7:3, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoic acid (2.51 g, yield: 92%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.25 (3 H, d, J = 6.8 Hz), 2.44 - 2.54 (1 H, m), 2.61 - 2.81 (1 H, m), 3.27 - 3.39 (1 H, m), 3.43 (3 H, s), 3.65 - 3.78 (2 H, m), 3.99 - 4.14 (2 H, m), 6.65 (1 H, d, J = 2.6 Hz), 6.85 (1 H, dd, J = 8.7, 2.4 Hz), 7.12 - 7.24 (1 H, m), 7.98 (1 H, d, J = 2.3 Hz), 8.22 - 8.28 (1 H, m).

Reference Example 46

A mixture of ethyl 3-[1-(2,4-difluorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoate (0.16 g), a 1N aqueous sodium hydroxide solution (4.0 ml), tetrahydrofuran (4.0 ml) and ethanol (4.0 ml) was stirred at 60°C for 30 min, 1N hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give 3-[1-(2,4-difluorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (140 mg, yield: 95%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.3 Hz), 2.63 (2 H, t, J = 7.4 Hz), 2.83 (2 H, t, J = 7.4 Hz), 4.62 - 4.74 (1 H,

m), 5.13 (2 H, s), 5.49 (1 H, s), 6.74 - 6.98 (3 H, m).

Reference Example 47

A mixed solution of ethyl 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoate (4.00 g), a 1N aqueous sodium hydroxide solution (18 ml), tetrahydrofuran (20 ml) and methanol (20 ml) was stirred at 50°C for 2 hr. 1N Hydrochloric acid (19 ml) and brine (30 ml) were added to the reaction mixture, and the mixture was extracted with ethyl acetate (60 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained crude crystals were recrystallized from hexane-ethyl acetate to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (3.54 g, yield: 82%) as colorless crystals. melting point 114-115°C.

Reference Example 48

A mixture of ethyl 3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]propanoate (1.00 g), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (30 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]propanoic acid (680 mg, yield: 74%) as colorless crystals. melting point 105-108°C.

Reference Example 49

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]acrylate (950 mg), a 1N aqueous sodium hydroxide solution (8.0 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (30 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from

ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]acrylic acid (790 mg, yield: 90%) as colorless crystals. melting point 170-171°C.

Reference Example 50

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]acrylate (600 mg), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (15 ml) and ethanol (15 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (30 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]acrylic acid (420 mg, yield: 75%) as colorless crystals. melting point 174-175°C.

Reference Example 51

A mixture of ethyl 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}propanoate (1.90 g), a 1N aqueous sodium hydroxide solution (10 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}propanoic acid (1.20 g, yield: 68%) as colorless crystals. melting point 117-119°C.

Reference Example 52

A mixture of ethyl 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoate (2.07 g), a 1N aqueous sodium hydroxide solution (13 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The

ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoic acid (1.70 g, yield: 88%) as colorless crystals. melting point 123-124°C.

Reference Example 53

A mixture of ethyl 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylate (4.00 g), a 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (40 ml) and ethanol (40 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylic acid (2.82 g, yield: 76%) as colorless crystals. melting point 176-179°C.

Reference Example 54

To a mixture of potassium tert-butoxide (132 g) and tetrahydrofuran (600 ml) was added dropwise a mixture of acetophenone (100 g) and diethyl oxalate (123 g), and the mixture was stirred at room temperature for 15 hr. Acetic acid (119 ml) and hydrazine monohydrate (45.8 g) were added to the reaction mixture, and the mixture was stirred with heating under reflux for 2 hr. After cooling to room temperature, the reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium carbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from diisopropyl ether to give ethyl 3-phenyl-1H-pyrazole-5-carboxylate (145 g, yield: 81%) as a brown solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.36 (3 H, t, J = 7.2 Hz), 4.36 (2 H, q, J = 7.2 Hz), 7.10 (1 H, s), 7.30 - 7.46 (3 H, m), 7.71 - 7.80 (2 H, m), 11.86 (1 H, brs).

Reference Example 55

A mixture of ethyl 3-phenyl-1H-pyrazole-5-carboxylate (70.0 g), 2,4-dichlorobenzyl chloride (69.6 g), potassium carbonate (53.7 g) and N,N-dimethylformamide (400 ml) was stirred at room temperature for 15 hr, the reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give ethyl 1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazole-5-carboxylate (61.0 g, yield: 50%) as brown crystals. melting point 104-107°C.

Reference Example 56

To a solution of ethyl 1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazole-5-carboxylate (60.0 g) in tetrahydrofuran (400 ml) was added a 1.5 M solution (267 ml) of diisobutylaluminum hydride in toluene at 0°C. The mixture was stirred at room temperature for 2 hr and methanol was added to quench the reaction. The reaction mixture was poured into a 10% aqueous Rochelle salt solution, and the mixture was stirred and extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give [1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]methanol (48.9 g, yield: 92%) as pale-brown crystals. melting point 140-141°C.

Reference Example 57

Under a nitrogen atmosphere, to a solution of oxalyl chloride (15.2 g) in dichloromethane (100 ml) was added dimethyl sulfoxide (28.1 g) at -78°C, and the mixture was stirred for 5 min. A solution of [1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]methanol (20.0 g) in dichloromethane (300 ml) was added. After stirring at -78°C for 1 hr, triethylamine (30.3 g) was added, and the reaction mixture was warmed to room temperature and further stirred for 1 hr. The

reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazole-5-carbaldehyde (13.3 g, yield: 67%) as pale-yellow crystals. melting point 135-137°C.

Reference Example 58

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (10.2 g) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 1.57 g), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazole-5-carbaldehyde (10.0 g) in tetrahydrofuran (60 ml) was added, and the mixture was stirred for 1 hr. A saturated aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]acrylate (11.5 g, yield: 95%) as colorless crystals. melting point 123-124°C.

Reference Example 59

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]acrylate (7.00 g), 5% palladium-carbon (860 mg) and tetrahydrofuran (100 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was crystallized from ethyl acetate-hexane to give ethyl 3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]propanoate (4.18 g, yield: 60%) as colorless crystals. melting point 91-93°C.

Reference Example 60

A mixture of ethyl 3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-

pyrazol-5-yl]propanoate (5.22 g), a 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (50 ml) and ethanol (50 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]propanoic acid (4.28 g, yield: 88%) as colorless crystals. melting point 160-161°C.

Reference Example 61

To a solution of ethyl 3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]propanoate (2.00 g), 2-methoxyethanol (887 mg) and tributylphosphine (2.37 g) in tetrahydrofuran (150 ml) was added 1,1'-(azodicarbonyl)dipiperidine (2.95 g), and the mixture was stirred at room temperature for 15 hr and concentrated. Diisopropyl ether was added to the residue, the resulting insoluble material was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:1, v/v) to give ethyl 3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]propanoate (1.70 g, yield: 73%) as a colorless oil.

A mixture of ethyl 3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]propanoate (1.70 g), a 1N aqueous sodium hydroxide solution (10 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]propanoic acid (1.48 g, yield: 94%) as colorless crystals. melting point 111-113°C.

Reference Example 62

To a solution of ethyl 3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]propanoate (1.00 g), benzyl alcohol (630 mg) and tributylphosphine (1.18 g) in tetrahydrofuran (70 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.47 g), and the mixture was stirred at room temperature for 15 hr and concentrated. Diisopropyl ether was added to the residue, the resulting insoluble material was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:4, v/v) to give ethyl 3-[3-(benzyloxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoate (510 mg, yield: 40%) as a colorless oil.

A mixture of ethyl 3-[3-(benzyloxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoate (510 mg), a 1N aqueous sodium hydroxide solution (3.0 ml), tetrahydrofuran (8.0 ml) and ethanol (8.0 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[3-(benzyloxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoic acid (420 mg, yield: 88%) as colorless crystals. melting point 98-101°C.

Reference Example 63

A mixture of methyl 3-hydroxypyrazole-5-carboxylate (48.2 g), potassium carbonate (51.6 g), 1-iodobutane (40.5 g) and N,N-dimethylformamide (300 ml) was stirred at room temperature for 12 hr. The reaction mixture was concentrated, and the concentrate was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from hexane to give methyl 3-butoxypyrazole-5-carboxylate (43.6 g, yield: 64%, containing isomer by about

10%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.41 - 1.54 (2 H, m), 1.71 - 1.81 (2 H, m), 3.91 (3 H, s), 4.16 (2 H, t, J = 6.6 Hz), 6.21 (1 H, s), 9.90 - 10.20 (1 H, brs).

Reference Example 64

A mixture of methyl 3-butoxypyrazole-5-carboxylate (5.00 g), 4-(trifluoromethyl)benzyl bromide (7.22 g), potassium carbonate (5.22 g) and N,N-dimethylformamide (50 ml) was stirred at room temperature for 15 hr. The reaction mixture was poured into water to partition the mixture between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:9, v/v) to give methyl 3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylate (5.79 g, yield: 64%, containing isomer by about 10%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.41 - 1.55 (2 H, m), 1.68 - 1.82 (2 H, m), 3.83 (3 H, s), 4.12 (2 H, t, J = 6.6 Hz), 5.65 (2 H, s), 6.25 (1 H, s), 7.33 (2 H, d, J = 8.1 Hz), 7.55 (2 H, d, J = 8.1 Hz).

Reference Example 65

A mixture of methyl 3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylate (5.79 g), a 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (60 ml) and ethanol (60 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylic acid (3.33 g, yield: 60%) as colorless crystals. melting point 128-129°C.

Reference Example 66

A mixture of N,O-dimethylhydroxylamine hydrochloride

(1.13 g), triethylamine (1.17 g) and N,N-dimethylformamide (30 ml) was stirred at room temperature for 30 min, 3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylic acid (3.30 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.22 g) and 1-hydroxybenzotriazole monohydrate (1.78 g) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogencarbonate, water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v) to give 3-butoxy-N-methoxy-N-methyl-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxamide (3.01 g, yield: 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.97 (3 H, t, J = 7.2 Hz), 1.41 - 1.55 (2 H, m), 1.70 - 1.81 (2 H, m), 3.27 (3 H, s), 3.55 (3 H, s), 4.15 (2 H, t, J = 6.6 Hz), 5.59 (2 H, s), 6.22 (1 H, s), 7.30 (2 H, d, J = 8.1 Hz), 7.53 (2 H, d, J = 8.1 Hz).

Reference Example 67

To a solution of 3-butoxy-N-methoxy-N-methyl-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxamide (3.00 g) in tetrahydrofuran (100 ml) was added a 1.5 M solution (11.7 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred for 1 hr. Methanol was added to quench the reaction. The reaction mixture was poured into a 10% aqueous Rochelle salt solution, and the mixture was stirred and extracted with diethyl ether. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:17, v/v) to give 3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carbaldehyde (2.31 g, yield: 91%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.97 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.70 - 1.82 (2 H, m), 4.16 (2 H, t, J = 6.5 Hz),

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5.61 (2 H, s), 6.29 (1 H, s), 7.37 (2 H, d, J = 8.6 Hz), 7.55 (2 H, d, J = 8.6 Hz), 9.71 (1 H, s).

Reference Example 68

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (2.38 g) in N,N-dimethylformamide (20 ml) was added sodium hydride (60% in oil, 368 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carbaldehyde (2.31 g) in tetrahydrofuran (15 ml) was added, and the mixture was stirred for 1 hr. The mixture was warmed to room temperature and further stirred for 1 hr. A saturated aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:17, v/v) to give ethyl (2E)-3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (2.02 g, yield: 72%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.69 - 1.81 (2 H, m), 4.12 (2 H, t, J = 6.6 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.33 (2 H, s), 6.01 (1 H, s), 6.28 (1 H, d, J = 15.8 Hz), 7.22 (2 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 15.8 Hz), 7.57 (2 H, d, J = 8.1 Hz).

Reference Example 69

A mixture of ethyl (2E)-3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (1.00 g), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated

brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (760 mg, yield: 82%) as colorless crystals. melting point 153-155°C.

Reference Example 70

A mixture of ethyl (2E)-3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (1.01 g), 5% palladium-carbon (250 mg) and tetrahydrofuran (20 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated to give ethyl 3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoate (950 mg, yield: 94%) as a colorless oil.

A mixture of ethyl 3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoate (950 mg), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (720 mg, yield: 66%) as colorless crystals. melting point 116-118°C.

Reference Example 71

A mixture of ethyl 3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]propanoate (2.00 g), tert-butyl bromoacetate (1.37 g), potassium carbonate (1.21 g) and N,N-dimethylformamide (30 ml) was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the concentrate was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica

gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v) to give ethyl 3-[3-(2-tert-butoxy-2-oxoethoxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoate (2.03 g, yield: 76%) as a colorless solid.

A mixture of ethyl 3-[3-(2-tert-butoxy-2-oxoethoxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoate and trifluoroacetic acid (20 ml) was stirred at room temperature for 1 hr. The reaction mixture was concentrated. The residue was crystallized from ethyl acetate-hexane to give {[1-(2,4-dichlorobenzyl)-5-(3-ethoxy-3-oxopropyl)-1H-pyrazol-3-yl]oxy}acetic acid (1.65 g, yield: 93%) as colorless crystals. melting point 129-131°C.

Reference Example 72

To a solution of {[1-(2,4-dichlorobenzyl)-5-(3-ethoxy-3-oxopropyl)-1H-pyrazol-3-yl]oxy}acetic acid (400 mg) in tetrahydrofuran (7.0 ml) was added N,N'-carbonyldiimidazole (178 mg), and the mixture was stirred at room temperature for 2 hr. Acetylhydrazine (296 mg) was added, and the mixture was further stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give ethyl 3-{3-[2-(2-acetylhydrazino)-2-oxoethoxy]-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl}propanoate (410 mg, yield: 90%) as colorless crystals. melting point 167-170°C.

Reference Example 73

Ethyl 3-{3-[2-(2-acetylhydrazino)-2-oxoethoxy]-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl}propanoate (410 mg), diphosphorus pentaoxide (510 mg), hexamethyldisiloxane (1.17 g) and toluene (20 ml) was stirred with heating under reflux for 3 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate and saturated brine, dried ($MgSO_4$), and concentrated. The residue

was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give ethyl 3-{1-(2,4-dichlorobenzyl)-3-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]-1H-pyrazol-5-yl}propanoate (270 mg, yield: 69%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.25 (3 H, t, J = 7.2 Hz), 2.54 (3 H, s), 2.55 - 2.62 (2 H, m), 2.74 - 2.83 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 5.20 (2 H, s), 5.33 (2 H, s), 5.62 (1 H, s), 6.56 (1 H, d, J = 8.4 Hz), 7.16 (1 H, dd, J = 2.1, 8.4 Hz), 7.39 (1 H, d, J = 2.1 Hz).

Reference Example 74

Under ice-cooling, to a solution of ethyl 3-{1-(2,4-dichlorobenzyl)-3-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]-1H-pyrazol-5-yl}propanoate (270 mg) in tetrahydrofuran (4.0 ml) was added a solution of lithium hydroxide monohydrate (28 mg) in water (1.0 ml). The mixture was stirred for 20 min, warmed to room temperature, and further stirred for 20 min. A solution of lithium hydroxide monohydrate (28 mg) in water (1.0 ml) was added to the reaction mixture, and the mixture was stirred at room temperature for 20 min. A 10% citric acid aqueous solution (50 ml) was added to quench the reaction. The reaction mixture was concentrated under reduced pressure to evaporate tetrahydrofuran, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$) and concentrated to give 3-{1-(2,4-dichlorobenzyl)-3-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]-1H-pyrazol-5-yl}propanoic acid (250 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (3 H, s), 2.59 - 2.67 (2 H, m), 2.74 - 2.82 (2 H, m), 5.19 (2 H, s), 5.34 (2 H, s), 6.55 (1 H, d, J = 8.1 Hz), 7.15 (1 H, dd, J = 2.1, 8.1 Hz), 7.38 (1 H, d, J = 2.1 Hz), 11.02 (1 H, brs).

Reference Example 75

A mixture of methyl 3-butoxypyrazole-5-carboxylate (7.28 g), 2-chloro-1-(chloromethyl)-4-(trifluoromethyl)benzene (38.9 g), potassium carbonate (7.61 g) and N,N-dimethylformamide (60

ml) was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:10, v/v) to give methyl 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylate (9.79 g, yield: 68%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.39 - 1.54 (2 H, m), 1.67 - 1.82 (2 H, m), 3.82 (3 H, s), 4.13 (2 H, t, J = 6.6 Hz), 5.76 (2 H, s), 6.32 (1 H, s), 6.66 (1 H, d, J = 8.1 Hz), 7.39 (1 H, dd, J = 1.2, 8.1 Hz), 7.64 (1 H, d, J = 1.2 Hz).

Reference Example 76

A mixture of methyl 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylate (9.79 g), a 1N aqueous sodium hydroxide solution (45 ml), tetrahydrofuran (90 ml) and ethanol (90 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylic acid (7.88 g, yield: 83%) as colorless crystals. melting point 158-160°C.

Reference Example 77

A mixture of N,O-dimethylhydroxylamine hydrochloride (2.42 g), triethylamine (2.51 g) and N,N-dimethylformamide (100 ml) was stirred at room temperature for 30 min, 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylic acid (7.79 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.75 g) and 1-hydroxybenzotriazole monohydrate (3.80 g) were added, and the

mixture was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogencarbonate, water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v) to give 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide (8.69 g, yield: 100%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.40 - 1.55 (2 H, m), 1.70 - 1.81 (2 H, m), 3.28 (3 H, s), 3.66 (3 H, s), 4.15 (2 H, t, J = 6.6 Hz), 5.68 (2 H, s), 6.29 (1 H, s), 6.70 (1 H, d, J = 8.1 Hz), 7.38 (1 H, d, J = 8.1 Hz), 7.61 (1 H, s).

Reference Example 78

To a solution of 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide (8.69 g) in tetrahydrofuran (250 ml) was added a 1.5 M solution (21 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred for 1 hr. Methanol was added to quench the reaction. The reaction mixture was poured into a 10% aqueous Rochelle salt solution, and the mixture was stirred and extracted with diethyl ether. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:4, v/v) to give 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carbaldehyde (6.31 g, yield: 84%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.40 - 1.54 (2 H, m), 1.69 - 1.81 (2 H, m), 4.16 (2 H, t, J = 6.6 Hz), 5.73 (2 H, s), 6.36 (1 H, s), 6.70 (1 H, d, J = 7.8 Hz), 7.39 (1 H, dd, J = 1.2, 7.8 Hz), 7.65 (1 H, d, J = 7.8 Hz), 9.75 (1 H, s).

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Reference Example 79

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (3.26 g) in N,N-dimethylformamide (25 ml) was added sodium hydride (60% in oil, 504 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carbaldehyde (3.50 g) in tetrahydrofuran (22 ml) was added, and the mixture was stirred for 1 hr. The mixture was warmed to room temperature and further stirred for 1 hr. A saturated aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:49 - 1:9, v/v) to give ethyl (2E)-3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (1.74 g, yield: 42%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.69 - 1.81 (2 H, m), 4.12 (2 H, t, J = 6.6 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.33 (2 H, s), 6.01 (1 H, s), 6.28 (1 H, d, J = 15.8 Hz), 7.22 (2 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 15.8 Hz), 7.57 (2 H, d, J = 8.1 Hz).

Reference Example 80

A mixture of ethyl (2E)-3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (1.86 g), a 1N aqueous sodium hydroxide solution (10 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-{3-

butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (730 mg, yield: 42%) as colorless crystals. melting point 172-174°C.

Reference Example 81

A mixture of ethyl (2E)-3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (1.70 g), 5% palladium-carbon (360 mg) and tetrahydrofuran (30 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated to give ethyl 3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoate (1.67 g, yield: 98%) as a pale-yellow oil.

A mixture of ethyl 3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoate (1.67 g), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (1.25 g, yield: 80%) as colorless crystals. melting point 125-126°C.

Reference Example 82

A mixture of ethyl 3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]propanoate (2.00 g), 2-(chloromethyl)pyridine (573 mg), potassium carbonate (1.01 g) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v) to give ethyl 3-[1-(2,4-dichlorobenzyl)-3-

(pyridin-2-ylmethoxy)-1H-pyrazol-5-yl]propanoate (1.00 g, yield: 79%) as a colorless solid.

A mixture of ethyl 3-[1-(2,4-dichlorobenzyl)-3-(pyridin-2-ylmethoxy)-1H-pyrazol-5-yl]propanoate (1.00 g), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, water (200 ml) was added, and the precipitated crystals were collected by filtration to give 3-[1-(2,4-dichlorobenzyl)-3-(pyridin-2-ylmethoxy)-1H-pyrazol-5-yl]propanoic acid (0.76 g, yield: 75%) as a white solid.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.46 - 2.56 (2 H, m), 2.67 - 2.77 (2 H, m), 5.15 (2 H, s), 5.20 (2 H, s), 5.72 (1 H, s), 6.62 (1 H, d, J = 8.4 Hz), 7.27 - 7.34 (1 H, m), 7.35 (1 H, dd, J = 2.1, 8.4 Hz), 7.43 (1 H, d, J = 7.8 Hz), 7.65 (1 H, d, J = 2.1 Hz), 7.77 - 7.84 (1 H, m), 8.51 - 8.56 (1 H, m), 12.30 (1 H, brs).

Reference Example 83

A mixture of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-hydroxy-1H-pyrazol-5-yl}acrylate (275 mg), bromomethylcyclopropane (560 mg), potassium carbonate (760 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the concentrate was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 1:4, v/v), concentrated and crystallized from ethyl acetate-hexane to give ethyl (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylate (690 mg, yield: 59%) as colorless crystals.

A mixture of ethyl (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylate (400 mg), a 1N aqueous sodium hydroxide solution (3.0 ml), tetrahydrofuran (6.0 ml) and ethanol (6.0 ml) was stirred at 50°C for 1 hr. The reaction mixture was

concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylic acid (300 mg, yield: 80%) as colorless crystals. melting point 195-196°C.

Reference Example 84

Ethyl (2E)-3-[1-(2,4-Dichlorobenzyl)-3-(methoxymethoxy)-1H-pyrazol-5-yl]acrylate (2.49 g), concentrated hydrochloric acid (0.15 ml) and methanol (30 ml) were stirred with heating under reflux for 5 hr. The reaction mixture was concentrated, and the residue was crystallized from diisopropyl ether-hexane-ethyl acetate to give ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]acrylate (2.41 g) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.31 (3 H, t, J = 7.2 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.28 (2 H, s), 5.95 (1 H, s), 6.32 (1 H, d, J = 15.6 Hz), 6.72 (1 H, d, J = 8.4 Hz), 7.17 (1 H, dd, J = 2.1, 8.4 Hz), 7.38 (1 H, d, J = 15.6 Hz), 7.41 (1 H, d, J = 2.1 Hz).

Reference Example 85

To a solution of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]acrylate (1.20 g), 2-methoxyethanol (533 mg) and tributylphosphine (1.42 g) in tetrahydrofuran (70 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.77 g), and the mixture was stirred at room temperature for 15 hr and concentrated. Diisopropyl ether was added to the residue, the resulting insoluble material was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:1, v/v) to give ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylate (850 mg, yield: 61%) as colorless crystals.

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-

methoxyethoxy)-1H-pyrazol-5-yl]acrylate (850 mg), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylic acid (300 mg, yield: 91%) as colorless crystals. melting point 171-172°C.

Reference Example 86

A mixture of methyl 3-hydroxy-1H-pyrazole-5-carboxylate (68.6 g), chloromethylmethyl ether (46.7 g), potassium carbonate (100 g) and N,N-dimethylformamide (350 ml) was stirred at room temperature for 15 hr, poured into water, and the mixture was extracted with ethyl acetate. The aqueous layer was extracted with chloroform, the extracts were combined, and the mixture was concentrated. The residue was dissolved in chloroform, and the solution was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:12 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give methyl 3-(methoxymethoxy)-1H-pyrazole-5-carboxylate (23.4 g, yield: 26%) as colorless crystals. melting point 54-55°C.

Reference Example 87

A mixture of methyl 3-(methoxymethoxy)-1H-pyrazole-5-carboxylate (23.4 g), 2-chloro-4-trifluoromethylbenzyl chloride (30.0 g), potassium carbonate (26.1 g) and N,N-dimethylformamide (120 ml) was stirred at room temperature for 15 hr, poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:10, v/v) to give methyl 1-[2-

chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazole-5-carboxylate (34.1 g, yield: 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.53 (3 H, s), 3.83 (3 H, s), 5.24 (2 H, s), 5.79 (2 H, s), 6.46 (1 H, s), 6.70 (1 H, d, J = 8.1 Hz), 7.43 (1 H, dd, J = 0.9, 8.1 Hz), 7.65 (1 H, d, J = 0.9 Hz).

Reference Example 88

A mixture of methyl 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazole-5-carboxylate (34.1 g), a 1N aqueous sodium hydroxide solution (150 ml), tetrahydrofuran (250 ml) and ethanol (250 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazole-5-carboxylic acid (28.1 g, yield: 86%) as colorless crystals. melting point 133-134°C.

Reference Example 89

A mixture of N,O-dimethylhydroxylamine hydrochloride (9.01 g), triethylamine (9.35 g) and N,N-dimethylformamide (300 ml) was stirred at room temperature for 30 min, 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazole-5-carboxylic acid (28.1 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (17.7 g) and 1-hydroxybenzotriazole monohydrate (14.2 g) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogencarbonate solution, water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl

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acetate-hexane (1:19 - 1:1, v/v) to give 1-[2-chloro-4-(trifluoromethyl)benzyl]-N-methoxy-3-(methoxymethoxy)-N-methyl-1H-pyrazole-5-carboxamide (29.1 g, yield: 93%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.29 (3 H, s), 3.53 (3 H, s), 3.67 (3 H, s), 5.25 (2 H, s), 5.70 (2 H, s), 6.41 (1 H, s), 6.75 (1 H, d, J = 8.1 Hz), 7.40 (1 H, d, J = 8.1 Hz), 7.62 (1 H, s).

Reference Example 90

To a solution of 1-[2-chloro-4-(trifluoromethyl)benzyl]-N-methoxy-3-(methoxymethoxy)-N-methyl-1H-pyrazole-5-carboxamide (29.1 g) in tetrahydrofuran (500 ml) was added a 1.5 M solution (71.0 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred for 1 hr. Methanol was added to quench the reaction. The reaction mixture was poured into a 10% aqueous Rochelle salt solution, and the mixture was stirred and extracted with diethyl ether. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v) to give 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazole-5-carbaldehyde (21.2 g, yield: 85%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.53 (3 H, s), 5.75 (2 H, s), 6.51 (1 H, s), 6.75 (1 H, d, J = 8.1 Hz), 7.40 (1 H, d, J = 8.1 Hz), 7.65 (1 H, s), 9.76 (1 H, s).

Reference Example 91

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (16.6 g) in N,N-dimethylformamide (100 ml) was added sodium hydride (60% in oil, 2.56 g), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazole-5-carbaldehyde (17.2 g) in tetrahydrofuran (110 ml) was added, and the mixture was stirred for 1 hr. The mixture was warmed to room temperature and further stirred for 1 hr. A saturated

aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:3, v/v) to give ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazol-5-yl}acrylate (12.4 g, yield: 60%) as a colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.30 (3 H, t, J = 7.2 Hz), 3.53 (3 H, s), 4.23 (2 H, t, J = 7.2 Hz), 5.23 (2 H, s), 5.43 (2 H, s), 6.18 (1 H, s), 6.32 (1 H, d, J = 15.5 Hz), 6.83 (1 H, d, J = 8.1 Hz), 7.39 (1 H, d, J = 15.5 Hz), 7.43 (1 H, d, J = 8.1 Hz), 7.66 (1 H, s).

Reference Example 92

Ethyl (2E)-3-{1-[2-Chloro-4-(trifluoromethyl)benzyl]-3-(methoxymethoxy)-1H-pyrazol-5-yl}acrylate (8.40 g), concentrated hydrochloric acid (0.30 ml) and methanol (70 ml) were stirred with heating under reflux for 5 hr. The reaction mixture was concentrated, and the residue was crystallized from diisopropyl ether-hexane to give ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-hydroxy-1H-pyrazol-5-yl}acrylate (6.53 g) as a white solid.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.30 (3 H, t, J = 7.2 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.36 (2 H, s), 5.98 (1 H, s), 6.34 (1 H, d, J = 15.8 Hz), 6.84 (1 H, d, J = 8.1 Hz), 7.36 (1 H, d, 8.1 Hz), 7.67 (1 H, s).

Reference Example 93

Ethyl (2E)-3-{1-[2-Chloro-4-(trifluoromethyl)benzyl]-3-hydroxy-1H-pyrazol-5-yl}acrylate (1.20 g), 2-iodopropane (653 mg), potassium carbonate (663 mg) and N,N-dimethylformamide (20 ml) were stirred at room temperature for 15 hr, the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated.

The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 7:3, v/v) to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}ethyl acrylate (1.08 g, 81%) as white crystals.

A mixture of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}ethyl acrylate (1.38 g), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}acrylic acid (1.22 g, yield: 95%) as colorless crystals. melting point 170-171°C.

Reference Example 94

To a solution of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-hydroxy-1H-pyrazol-5-yl}acrylate (500 mg), (3-methyloxetan-3-yl)methanol (160 mg) and tributylphosphine (540 mg) in tetrahydrofuran (15 ml) was added 1,1'-(azodicarbonyl)dipiperidine (620 mg), and the mixture was stirred at room temperature for 2 hr and concentrated. Diisopropyl ether was added to the residue, the resulting insoluble material was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (3:17 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-[(3-methyloxetan-3-yl)methoxy]-1H-pyrazol-5-yl}acrylate (560 mg, yield: 91%) as a colorless oil.

A mixture of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-[(3-methyloxetan-3-yl)methoxy]-1H-pyrazol-5-yl}acrylate (560 mg), a 1N aqueous sodium hydroxide

solution (2.4 ml), tetrahydrofuran (7 ml) and ethanol (7 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-[(3-methyloxetan-3-yl)methoxy]-1H-pyrazol-5-yl}acrylic acid (425 mg, yield: 82%) as colorless crystals. melting point 148-149°C.

Reference Example 95

To a solution (heated to 60°C) of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-hydroxy-1H-pyrazol-5-yl]acrylate (1.50 g), tetrahydro-2H-pyran-4-ol (893 mg) and tributylphosphine (1.77 g) in tetrahydrofuran (60 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.77 g), and the mixture was stirred for 15 hr. After cooling to room temperature, the reaction mixture was concentrated. Diisopropyl ether was added to the residue, the resulting insoluble material was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 1:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylate (1.47 g, yield: 79%) as colorless crystals.

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylate (1.50 g), a 1N aqueous sodium hydroxide solution (8.0 ml), tetrahydrofuran (15 ml) and ethanol (15 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give

(2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylic acid (1.35 g, yield: 96%) as colorless crystals. melting point 191-192°C.

Reference Example 96

To a solution (heated to 60°C) of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-hydroxy-1H-pyrazol-5-yl}acrylate (1.26 g), tetrahydro-2H-pyran-4-ol (687 mg) and tributylphosphine (1.36 g) in tetrahydrofuran (50 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.70 g), and the mixture was stirred for 15 hr. After cooling to room temperature, the reaction mixture was concentrated. Diisopropyl ether was added to the residue, the resulting insoluble material was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 1:3, v/v) to give ethyl (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylate (1.16 g, yield: 75%) as colorless crystals.

A mixture of ethyl (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylate (1.16 g), a 1N aqueous sodium hydroxide solution (5.0 ml), tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylic acid (1.07 g, yield: 98%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.73 - 1.87 (2 H, m), 2.00 - 2.13 (2 H, m), 3.48 - 3.63 (2 H, m), 3.92 - 4.04 (2 H, m), 4.64 - 4.76 (1 H, m), 5.41 (2 H, s), 6.09 (1 H, s), 6.29 (1 H, d, J = 15.6 Hz), 6.77 (1 H, d, J = 8.1Hz), 7.44 (1 H, d, J = 8.1Hz), 7.45

(1 H, d, J = 15.6 Hz), 7.67 (1 H, s).

Reference Example 97

To a mixture of potassium tert-butoxide (94.1 g) and tetrahydrofuran (500 ml) was added dropwise a mixture of acetylcyclopropane (50.0 g) and diethyl oxalate (87.8 g), and the mixture was stirred at room temperature for 15 hr. Acetic acid (81.3 ml) and hydrazine monohydrate (32.7 g) were added to the reaction mixture, and the mixture was stirred with heating under reflux for 2 hr. After cooling to room temperature, the reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium carbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from diisopropyl ether to give ethyl 3-cyclopropyl-1H-pyrazole-5-carboxylate (64.5 g, yield: 60%) as brown crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.68 - 0.82 (2 H, m), 0.90 - 1.06 (2 H, m), 1.34 (3 H, t, J = 7.2 Hz), 1.88 - 2.04 (1 H, m), 4.36 (2 H, q, J = 7.2 Hz), 6.45 (1 H, s), 11.30 (1 H, brs).

Reference Example 98

A mixture of ethyl 3-cyclopropyl-1H-pyrazole-5-carboxylate (20.0 g), 2-chloro-4-trifluoromethylbenzyl chloride (28.0 g), potassium carbonate (23.0 g) and N,N-dimethylformamide (200 ml) was stirred at room temperature for 15 hr, concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v) to give ethyl 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazole-5-carboxylate (23.2 g, yield: 56%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.72 - 0.80 (2 H, m), 0.92 - 1.02 (2 H, m), 1.29 (3 H, t, J = 7.2 Hz), 1.90 - 2.02 (1H, m), 4.25 (2 H, q, J = 7.2 Hz), 5.82 (2 H, s), 6.53 (1 H, d, J = 8.1Hz),

6.62 (1 H, s), 7.38 (1 H, d, J = 8.1Hz), 7.64 (1 H, s).

Reference Example 99

To a solution of ethyl 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazole-5-carboxylate (23.2 g) in tetrahydrofuran (300 ml) was added a 1.5 M solution (104 ml) of diisobutylaluminum hydride in toluene at 0°C. The mixture was stirred at room temperature for 1 hr, and sodium sulfate 10 hydrate was added to quench the reaction. The insoluble material was filtered off, and the filtrate was concentrated. The residue was dissolved in ethyl acetate, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give {1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}methanol (17.2 g, yield: 84%) as colorless crystals. ^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.68 - 0.75 (2 H, m), 0.88 - 0.98 (2 H, m), 1.63 (1 H, t, J = 5.7 Hz), 1.88 - 1.99 (1 H, m), 4.55 (2 H, d, J = 5.7 Hz), 5.45 (2 H, s), 5.96 (1 H, s), 6.66 (1 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 8.1 Hz), 7.63 (1 H, s).

Reference Example 100

Under a nitrogen atmosphere, to a solution of oxalyl chloride (13.1 g) in dichloromethane (150 ml) was added dimethylsulfoxide (12.1 g) at -78°C, and the mixture was stirred for 5 min. A solution of {1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}methanol (17.1 g) in dichloromethane (200 ml) was added. After stirring at -78°C for 1 hr, triethylamine (26.2 g) was added, and the reaction mixture was warmed to room temperature and further stirred for 1 hr. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazole-5-carbaldehyde (14.3 g, yield: 84%) as pale-yellow crystals. melting point 94-96°C.

Reference Example 101

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (14.6 g) in N,N-dimethylformamide (100 ml) was added sodium hydride (60% in oil, 2.26 g), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazole-5-carbaldehyde (14.3 g) in tetrahydrofuran (100 ml) was added, and the mixture was stirred for 1 hr. The reaction mixture was warmed to room temperature and further stirred for 1 hr. A saturated aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:3, v/v) to give ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}acrylate (16.9 g, yield: 97%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.72 - 0.80 (2 H, m), 0.92 - 1.01 (2 H, m), 1.30 (3 H, t, J = 7.2 Hz), 1.88 - 2.00 (1 H, m), 4.22 (2 H, q, J = 7.2 Hz), 5.49 (2 H, s), 6.29 (1 H, d, J = 15.8 Hz), 6.66 (1 H, d, J = 8.1 Hz), 7.38 (1 H, d, J = 15.8 Hz), 7.42 (1 H, d, J = 8.1 Hz), 7.66 (1 H, s).

Reference Example 102

A mixture of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}acrylate (8.90 g), 5% palladium-carbon (1.91 g) and tetrahydrofuran (15 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (80 ml), ethanol (80 ml) and 1N aqueous sodium hydroxide solution (40 ml) were added, and the mixture was stirred at 50°C for 1 hr. The reaction mixture was

concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-diisopropyl ether to give 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}propanoic acid (1.80 g, yield: 86%, containing 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-propyl-1H-pyrazol-5-yl}propanoic acid by 9%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.66 - 0.74 (2 H, m), 0.87 - 0.97 (2 H, m), 1.85 - 1.98 (1 H, m), 2.60 - 2.67 (2 H, m), 2.72 - 2.79 (2 H, m), 5.36 (2 H, s), 5.80 (1 H, s), 6.59 (1 H, d, J = 8.1 Hz), 7.40 (1 H, dd, J = 0.9, 8.1 Hz), 7.66 (1 H, d, J = 0.9 Hz).

Reference Example 103

A mixture of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}acrylate (8.00 g), a 1N aqueous sodium hydroxide solution (40 ml), tetrahydrofuran (80 ml) and ethanol (80 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}acrylic acid (6.40 g, yield: 86%) as a white solid. melting point 191-192°C.

Reference Example 104

A mixture of ethyl (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylate (690 mg), 5% palladium-carbon (130 mg) and tetrahydrofuran (15 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated to give ethyl 3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-

(cyclopropylmethoxy)-1H-pyrazol-5-yl]propanoate (650 mg, yield: 94%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.28 - 0.37 (2 H, m), 0.54 - 0.64 (2 H, m), 1.18 - 1.32 (4 H, m), 2.53 - 2.64 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 5.26 (2 H, s), 5.59 (1 H, s), 6.68 (1 H, d, J = 8.1 Hz), 7.42 (1 H, d, J = 8.1 Hz), 7.64 (1 H, s).

Reference Example 105

A mixture of ethyl 3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]propanoate (650 mg), a 1N aqueous sodium hydroxide solution (4.0 ml), tetrahydrofuran (8.0 ml) and ethanol (8.0 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (50 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]propanoic acid (510 mg, yield: 84%) as colorless crystals. melting point 115-116°C.

Reference Example 106

To a mixture of potassium tert-butoxide (64.8 g) and tetrahydrofuran (500 ml) was added dropwise a mixture of 3,3-dimethyl-2-butanone (41.0 g) and diethyl oxalate (60.4 g), and the mixture was stirred at room temperature for 15 hr. Acetic acid (56.0 ml) and hydrazine monohydrate (22.5 g) were added to the reaction mixture, and the mixture was stirred with heating under reflux for 2 hr. After cooling to room temperature, the reaction mixture was concentrated, and the residue was poured into water. The resulting precipitate was collected by filtration to give ethyl 3-tert-butyl-1H-pyrazole-5-carboxylate (65.6 g, yield: 82%) as an orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.278 (9 H, s), 1.282 (3 H, t, J = 7.2 Hz), 4.25 (2 H, q, J = 7.2 Hz), 6.49 (1 H, brs), 13.22 (1 H, brs).

Reference Example 107

A mixture of ethyl 3-tert-butyl-1H-pyrazole-5-carboxylate (20.0 g), 2-chloro-4-trifluoromethylbenzyl chloride (24.1 g), potassium carbonate (21.1 g) and N,N-dimethylformamide (200 ml) was stirred at room temperature for 15 hr, and the reaction mixture was concentrated. The residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:6, v/v) to give ethyl 3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylate (36.8 g, yield: 93%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.2 Hz), 1.34 (9 H, s), 4.25 (2 H, q, J = 7.2 Hz), 5.85 (2 H, s), 6.43 (1 H, d, J = 8.1Hz), 6.83 (1 H, s), 7.37 (1 H, d, J = 8.1Hz), 7.64 (1 H, s).

Reference Example 108

To a solution of ethyl 3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carboxylate (23.2 g) in tetrahydrofuran (400 ml) was added a 1.5 M solution (158 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred at room temperature for 1 hr. Sodium sulfate 10 hydrate was added to quench the reaction. The insoluble material was filtered off, and the filtrate was dried ($MgSO_4$) and concentrated. The residue was crystallized from ethyl acetate-hexane to give {3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}methanol (7.69 g, yield: 23%) as colorless crystals. melting point 115-117°C.

Reference Example 109

Under a nitrogen atmosphere, to a solution of oxalyl chloride (7.47 g) in dichloromethane (50 ml) was added dimethylsulfoxide (6.89 g) at -78°C, and the mixture was stirred for 5 min. A solution of {3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}methanol (10.2 g) in

dichloromethane (80 ml) was added. After stirring at -78°C for 1 hr, triethylamine (14.9 g) was added, and the reaction mixture was warmed to room temperature and further stirred for 1 hr. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carbaldehyde (8.16 g, yield: 81%) as pale-yellow crystals. melting point 147-149°C.

Reference Example 110

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (7.50 g) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 1.16 g), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazole-5-carbaldehyde (8.16 g) in tetrahydrofuran (50 ml) was added, and the mixture was stirred for 1 hr. The reaction mixture was warmed to room temperature and further stirred for 1 hr. A saturated aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:4, v/v) to give ethyl (2E)-3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (9.82 g, yield: 100%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.2 Hz), 1.33 (9 H, s), 4.21 (2 H, q, J = 7.2 Hz), 5.53 (2 H, s), 6.32 (1 H, d, J = 15.8 Hz), 6.56 (1 H, d, J = 8.4 Hz), 7.37 (1 H, d, J = 15.8 Hz), 7.41 (1 H, d, J = 8.4 Hz), 7.66 (1 H, s).

Reference Example 111

A mixture of ethyl (2E)-3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (3.00 g), a 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (40 ml) and ethanol (40 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (2E)-3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (2.24 g, yield: 80%) as colorless crystals. melting point 175-176°C.

Reference Example 112

A mixture of ethyl (2E)-3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylate (3.00 g), 5% palladium-carbon (500 mg) and tetrahydrofuran (50 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated to give ethyl 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoate (2.53 g, yield: 84%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.2 Hz), 1.31 (9 H, s), 2.55 - 2.65 (2 H, m), 2.72 - 2.82 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 5.39 (2 H, s), 6.00 (1 H, s), 6.47 (1 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 8.1 Hz), 7.63 (1 H, s).

Reference Example 113

A mixture of ethyl 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoate (2.53 g), a 1N aqueous sodium hydroxide solution (15 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (200 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated.

The residue was crystallized from ethyl acetate-hexane to give 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (2.08 g, yield: 88%) as colorless crystals. melting point 128-129°C.

Reference Example 114

A mixture of tert-butyl ({(E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]vinyl}sulfonyl)carbamate (1.03 g) and trifluoroacetic acid (20 ml) was stirred at room temperature for 1 hr and the reaction mixture was concentrated. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethylenesulfonamide (710 mg, yield: 87%) as colorless crystals. melting point 158-160°C.

Reference Example 115

A mixture of (E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethylenesulfonamide (350 mg), 5% palladium carbon (140 mg) and tetrahydrofuran (15 ml) was hydrogenated at room temperature under atmospheric pressure for 15 hr. The reaction mixture was filtrated, and the filtrate was concentrated. A mixture of the residue, 5% palladium-carbon (200 mg) and tetrahydrofuran (15 ml) was hydrogenated again at room temperature under atmospheric pressure for 15 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was crystallized from ethyl acetate-hexane to give 2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethanesulfonamide (260 mg, yield: 74%) as colorless crystals. melting point 142-143°C.

Reference Example 116

A mixture of tert-butyl ({(E)-2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]vinyl}sulfonyl)carbamate (1.55 g) and trifluoroacetic acid (15 ml) was stirred at room

temperature for 1 hr, and the reaction mixture was concentrated. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give (E)-2-[1-(2,4-dichlorobenzyl)-3-butoxy-1H-pyrazol-5-yl]ethylenesulfonamide (1.10 g, yield: 89%) as colorless crystals. melting point 105-108°C.

Reference Example 117

A mixture of (E)-2-[1-(2,4-dichlorobenzyl)-3-butoxy-1H-pyrazol-5-yl]ethylenesulfonamide (1.35 g), 5% palladium-carbon (920 mg) and tetrahydrofuran (50 ml) was hydrogenated at room temperature under atmospheric pressure for 24 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was crystallized from ethyl acetate-hexane to give 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (1.10 g, yield: 81%) as colorless crystals. melting point 134-136°C.

Reference Example 118

To a solution of ethyl 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}propionate (5.70 g) in tetrahydrofuran (15 ml) and ethanol (15 ml) was added a 1N aqueous sodium hydroxide solution (29.0 ml), and the mixture was stirred at 50°C for 30 min. 1N Hydrochloric acid (29.0 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}propionic acid (4.09 g, yield: 77%) as white fine needles. melting point 121.5-122.0°C.

Reference Example 119

To a solution of methyl 3-butoxy-1-(2,4-dichlorobenzyl)-

1H-pyrazole-5-carboxylate (41.63 g) in tetrahydrofuran (200 ml) was added a 1.5 M solution (300 ml) of diisobutylaluminum hydride in toluene under ice-cooling, and the mixture was stirred for 10 min. A saturated aqueous ammonium chloride solution (85.0 ml) was added to the reaction mixture, and the precipitated solid was filtered off and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:2, v/v) to give [3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]methanol (24.51 g, yield: 64%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.95 (3 H, t, J = 7.3 Hz), 1.20 - 1.53 (2 H, m), 1.66 - 1.89 (2 H, m), 4.05 - 4.21 (2 H, m), 4.47 - 4.63 (2 H, m), 5.28 (2 H, d, J = 1.5 Hz), 5.72 (1 H, d, J = 2.1 Hz), 6.59 - 6.68 (1 H, m), 7.14 (1 H, d, J = 8.5 Hz), 7.34 - 7.41 (1 H, m).

Reference Example 120

To a solution of [3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]methanol (1.71 g) in tetrahydrofuran (40 ml) were added tributylphosphine (2.40 ml), acetone cyanhydrin (0.70 ml) and 1,1'-azodicarbonyldipiperidine (2.40 g), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:3, v/v) to give a yellow oil.

To a solution of the obtained oil in ethanol (25 ml) was added 4N aqueous sodium hydroxide solution (13.0 ml), and the mixture was stirred with heating under reflux for 1.5 hr. After cooling to room temperature, 6N hydrochloric acid (9.0 ml) was added to the reaction mixture, and the mixture was diluted with toluene, concentrated, and dissolved in ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave [3-

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butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acetic acid (890 mg, yield: 48%) as white crystals. melting point 105-108°C.

Reference Example 121

To a solution of ethyl [3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylate (6.31 g) in tetrahydrofuran (100 ml) was added 5% palladium-carbon (4.30 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated and the filtrate was concentrated to give pale yellow oil.

To a solution of the obtained oil in tetrahydrofuran (100 ml) was added a 1.5 M solution (40 ml) of diisobutylaluminum hydride in toluene under ice-cooling, and the mixture was stirred for 10 min. A saturated aqueous ammonium chloride solution (12.0 ml) was added to the reaction mixture, and the precipitated solid was filtered off and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give a pale-yellow oil.

To a solution of the obtained oil in tetrahydrofuran (100 ml) were added tributylphosphine (5.90 ml), acetone cyanhydrin (2.0 ml) and 1,1'-azodicarbonyldipiperidine (5.31 g), and the mixture was stirred at room temperature for 1 hr, and at 50°C for 30 min. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:4, v/v) to give a pale-yellow oil.

To a solution of the obtained oil in ethanol (30 ml) was added 4N aqueous sodium hydroxide solution (5.0 ml), and the mixture was stirred with heating under reflux for 1 hr and 20 min. Then a 4N aqueous sodium hydroxide solution (2.5 ml) was added, and the mixture was stirred overnight with heating under reflux. After cooling to room temperature, 6N hydrochloric acid (5.0 ml) was added to the reaction mixture,

and the mixture was diluted with toluene, concentrated, and dissolved in ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give 4-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]butanoic acid (2.86 g, yield: 47%) as an orange oil. A part thereof was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave white fine needles. melting point 60.5-61.0°C.

Reference Example 122

4-[3-Butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]butanoic acid (630 mg) was added to a borane-tetrahydrofuran complex 1.0 M tetrahydrofuran solution (6.0 ml), and the mixture was stirred at room temperature for 30 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v) to give a colorless oil.

To a solution of the obtained oil in tetrahydrofuran (20 ml) were added tributylphosphine (0.80 ml), acetone cyanhydrin (0.25 ml) and 1,1'-azodicarbonyldipiperidine (0.80 g), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give a colorless oil.

To a solution of the obtained oil in ethanol (5 ml) was added a 4N aqueous sodium hydroxide solution (4.0 ml), and the mixture was stirred with heating under reflux for 3 hr. Then, a 8N aqueous sodium hydroxide solution (3.0 ml) was added, and the mixture was further stirred with heating under reflux for

4 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was diluted with toluene, concentrated, and dissolved in ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give 5-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]pentanoic acid (433 mg, yield: 63%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.95 (3 H, t, J = 7.4 Hz), 1.35 - 1.85 (8 H, m), 2.32 (2 H, t, J = 6.9 Hz), 2.44 (2 H, t, J = 7.1 Hz), 4.10 (2 H, q, J = 6.7 Hz), 5.15 (2 H, s), 5.55 (1 H, s), 6.56 (1 H, d, J = 8.5 Hz), 7.14 (1 H, dd, J = 8.5, 2.1 Hz), 7.37 (1 H, d, J = 2.1 Hz).

Reference Example 123

To a mixture of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-hydroxy-1H-pyrazol-5-yl}acrylate (1.49 g), 2-methoxyethanol (0.347 ml), tributylphosphine (2.49 ml) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (2.02 g) at 50°C, and the mixture was stirred for 1 hr. The reaction solution was concentrated, diisopropyl ether was added to the residue, and the insoluble material was filtered off. The mother liquor was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:100 - 1:4, v/v) to give a colorless oil (1.31 g).

A mixture of the obtained oil, a 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 8 hr, 1N hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained crude crystals were recrystallized from tetrahydrofuran-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylic acid (1.14 g, yield: 70%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.44 (3 H, s), 3.66 - 3.81 (2 H, m),

4.22 - 4.40 (2 H, m), 5.41 (2 H, s), 6.13 (1 H, s), 6.29 (1 H, d, J = 15.8 Hz), 6.77 (1 H, d, J = 8.1 Hz), 7.36 - 7.52 (2 H, m), 7.66 (1 H, d, J = 0.9 Hz).

Reference Example 124

Under ice-cooling, to a mixture of methyl 3-butoxypyrazole-5-carboxylate (43.1 g), potassium carbonate (36.0 g) and N,N-dimethylformamide (300 ml) was added 2,4-dichlorobenzyl chloride (33.2 ml), and the mixture was stirred at room temperature for 12 hr. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:15, v/v) to give methyl 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carboxylate (56.0 g, yield: 72%, containing isomer by about 10%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.40 - 1.53 (2 H, m), 1.69 - 1.79 (2 H, m), 3.81 (3 H, s), 4.12 (2 H, t, J = 6.6 Hz), 5.67 (2 H, s), 6.29 (1 H, s), 6.53 (1 H, d, J = 8.7 Hz), 7.11 (1 H, dd, J = 2.1, 8.1 Hz), 7.38 (1 H, d, J = 2.1 Hz).

Reference Example 125

To a mixture of methyl 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carboxylate (55.6 g), tetrahydrofuran (200 ml) and methanol (100 ml) was added a solution of sodium hydroxide (12.5 g) in water (100 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, 1N hydrochloric acid (320 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carboxylic acid (33.6 g, yield: 62%) as colorless crystals. melting point 154-155°C.

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Reference Example 126

A mixture of N,O-dimethylhydroxylamine hydrochloride (11.4 g), triethylamine (11.9 g) and N,N-dimethylformamide (300 ml) was stirred at room temperature for 30 min, 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carboxylic acid (33.6 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (22.5 g) and 1-hydroxybenzotriazole monohydrate (18.0 g) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, The residue was dissolved in ethyl acetate, and the mixture was washed with water, 1N hydrochloric acid, an aqueous potassium carbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:8 - 1:2, v/v) to give 3-butoxy-1-(2,4-dichlorobenzyl)-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide (37.4 g, yield: 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.40 - 1.53 (2 H, m), 1.69 - 1.79 (2 H, m), 3.28 (3 H, s), 3.63 (3 H, s), 4.14 (2 H, t, J = 6.6 Hz), 5.59 (2 H, s), 6.24 (1 H, s), 6.60 (1 H, d, J = 8.1 Hz), 7.11 (1 H, dd, J = 2.1, 8.4 Hz), 7.35 (1 H, d, J = 2.1 Hz).

Reference Example 127

To a solution of 3-butoxy-1-(2,4-dichlorobenzyl)-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide (37.4 g) in tetrahydrofuran (500 ml) was added a 1.5 M solution (97 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred for 1 hr. Sodium sulfate 10 hydrate (50.0 g) was added to quench the reaction. The reaction mixture was stirred at room temperature for 5 hr, the insoluble material was filtrated, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:10, v/v) to give 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carbaldehyde (29.9 g, yield: 94%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.97 (3 H, t, J = 7.2 Hz), 1.40 - 1.53 (2 H, m), 1.70 - 1.80 (2 H, m), 4.15 (2 H, t, J = 6.6 Hz), 5.64 (2 H, s), 6.33 (1 H, s), 6.59 (1 H, d, J = 8.1 Hz), 7.12 (1 H, d, J = 2.1, 8.1 Hz), 7.39 (1 H, d, J = 8.1 Hz), 9.74 (1 H, s).

Reference Example 128

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (10.3 g) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 1.59 g), and the mixture was stirred at room temperature for 30 min. The reaction mixture was ice-cooled, a solution of 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carbaldehyde (10.0 g) in tetrahydrofuran (30 ml) was added, and the mixture was stirred for 1 hr. The mixture was warmed to room temperature and further stirred for 30 min. The reaction mixture was concentrated, a saturated aqueous ammonium chloride solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:100 ~ 1:4, v/v) to give ethyl (2E)-3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylate (12.1 g, yield: 100%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.69 - 1.80 (2 H, m), 4.12 (2 H, t, J = 6.6 Hz), 4.22 (2 H, q, J = 7.2 Hz), 5.33 (2 H, s), 6.02 (1 H, s), 6.28 (1 H, d, J = 15.8 Hz), 6.65 (1 H, d, J = 8.4 Hz), 7.15 (1 H, dd, J = 2.1, 8.4 Hz), 7.39 (1 H, d, J = 15.8 Hz), 7.40 (1 H, d, J = 2.1 Hz).

Reference Example 129

A mixture of ethyl (2E)-3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylate (8.00 g), 5% palladium-carbon (1.00 g) and tetrahydrofuran (100 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was

concentrated to give ethyl 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoate (8.01 g, yield: 60%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.95 (3 H, t, J = 7.3 Hz), 1.24 (3 H, t, J = 7.2 Hz), 1.38 - 1.54 (2 H, m), 1.66 - 1.78 (2 H, m), 2.52 - 2.64 (2 H, m), 2.72 - 2.82 (2 H, m), 4.09 (2 H, t, J = 6.7 Hz), 4.12 (2 H, q, J = 7.2 Hz), 5.19 (2 H, s), 5.54 (1 H, s), 6.54 (1 H, d, J = 8.3 Hz), 7.15 (1 H, dd, J = 2.1, 8.3 Hz), 7.38 (1 H, d, J = 2.1 Hz).

Reference Example 130

To a solution (100 ml) of 2-hydroxy-4-(methoxymethoxy)benzaldehyde (11.9 g) in N,N-dimethylformamide were added benzyl bromide (8.5 ml) and potassium carbonate (10.8 g) at room temperature, and the mixture was stirred at 80°C for 1 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated to give an oil. To a solution (150 ml) of ethyl diethylphosphonoacetate (15.0 ml) in tetrahydrofuran was added sodium hydride (60% in oil, 3.3 g) at room temperature, and the mixture was stirred for 30 min. A solution (50 ml) of the oil in tetrahydrofuran obtained earlier was added dropwise to this reaction mixture, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5, v/v) to give ethyl (2E)-3-[2-(benzyloxy)-4-(methoxymethoxy)phenyl]acrylate as a yellow oil (21.6 g, yield: 96%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.32 (3 H, t, J = 7.2 Hz), 3.46 (3 H, s), 4.23 (2 H, q, J = 7.2 Hz), 5.14 (2 H, s), 5.16 (2 H, s), 6.44 (1 H, d, J = 16.2 Hz), 6.65 - 6.69 (2 H, m), 7.28 - 7.49

(6 H, m), 8.00 (1 H, d, J = 16.2 Hz).

Reference Example 131

To an ethyl (2E)-3-[2-(benzyloxy)-4-(methoxymethoxy)phenyl]acrylate (4.0 g) in tetrahydrofuran-ethanol mixed solution (1:1, v/v, 100 ml) was added 10% palladium-carbon (0.5 g), and the mixture was stirred under a hydrogen atmosphere for 3 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:5, v/v) to give ethyl 3-[2-hydroxy-4-(methoxymethoxy)phenyl]propanoate as a colorless oil (2.8 g, yield: 95%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.24 (3 H, t, J = 7.2 Hz), 2.62 - 2.71 (2 H, m), 2.78 - 2.89 (2 H, m), 3.46 (3 H, s), 4.15 (2 H, q, J = 7.2 Hz), 5.12 (2 H, s), 6.52 - 6.64 (2 H, m), 6.97 (1 H, d, J = 8.3 Hz), 7.42 (1 H, s).

Reference Example 132

To a solution (30 ml) of ethyl 3-[2-hydroxy-4-(methoxymethoxy)phenyl]propanoate (1.27 g) in N,N-dimethylformamide was added sodium hydride (60% in oil, 240 mg) at room temperature, and the mixture was stirred for 30 min. 2,3-Dichloro-5-(trifluoromethyl)pyridine (0.80 ml) was added to the reaction mixture, and the mixture was stirred at room temperature for 3 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:10, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propanoate as a colorless oil (1.60 g, yield: 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 2.52 - 2.64 (2 H, m), 2.71 - 2.83 (2 H, m), 3.47 (3 H, s), 4.09 (2 H, q, J = 7.2 Hz), 5.15 (2 H, s), 6.82 (1 H, d, J = 2.6 Hz), 6.93

(1 H, dd, J = 8.5, 2.5 Hz), 7.24 (1 H, d, J = 8.5 Hz), 7.97 - 8.00 (1 H, m), 8.22 - 8.30 (1 H, m).

Reference Example 133

To a solution of 2-chloro-4-trifluoromethylbenzyl alcohol (38.8 g) and pyridine (3.0 ml) in diethyl ether (320 ml)-tetrahydrofuran (80 ml) was added thionyl chloride (32.8 g), and the mixture was stirred at room temperature for 15 hr. The reaction solution was concentrated, water was poured into the residue and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:25 - 1:12, v/v) to give 2-chloro-4-trifluoromethylbenzyl chloride (38.9 g, yield: 92%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:4.72 (2 H, s), 7.51 - 7.57 (1 H, m), 7.60 - 7.70 (2 H, m).

Reference Example 134

A solution (50 ml) of ethyl (2E)-3-[2-(benzyloxy)-4-hydroxyphenyl]acrylate (5.1 g) in N,N-dimethylformamide was added 2-iodopropane (2.0 ml) and potassium carbonate (3.1 g), and the mixture was stirred at 60°C for 1.5 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5, v/v) to give ethyl (2E)-3-[2-(benzyloxy)-4-isopropoxyphenyl]acrylate as a colorless oil (5.0 g, yield: 86%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.27 - 1.35 (9 H, m), 4.23 (2 H, q, J = 7.0 Hz), 4.46 - 4.61 (1 H, m), 5.13 (2 H, s), 6.38 - 6.54 (3 H, m), 7.28 - 7.51 (6 H, m), 8.00 (1 H, d, J = 16.2 Hz).

Reference Example 135

To ethyl (2E)-3-[2-(benzyloxy)-4-

isopropoxyphenyl]acrylate (5.0 g) in a tetrahydrofuran-ethanol mixed solution (1:1, v/v, 100 ml) was added 10% palladium-carbon (0.5 g), and the mixture was stirred under a hydrogen atmosphere for 2 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl 3-(2-hydroxy-4-isopropoxyphenyl)propanoate as a pale yellow oil (3.3 g, yield: 89%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.24 (3 H, t, J = 7.2 Hz), 1.31 (6 H, d, J = 6.0 Hz), 2.63 - 2.72 (2 H, m), 2.76 - 2.86 (2 H, m), 4.15 (2 H, q, J = 7.2 Hz), 4.40 - 4.55 (1 H, m), 6.38 - 6.48 (2 H, m), 6.94 (1 H, d, J = 8.3 Hz), 7.43 (1 H, s).

Reference Example 136

To a solution (60 ml) of ethyl 3-(2-hydroxy-4-isopropoxyphenyl)propanoate (1.51 g) in N,N-dimethylformamide was added sodium hydride (60% in oil, 312 mg) at room temperature, and the mixture was stirred for 30 min. 2,3-Dichloro-5-(trifluoromethyl)pyridine (1.56 g) was added to this reaction mixture, and the mixture was stirred at 60°C for 15 min. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:15, v/v) to give ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propanoate as a colorless oil (2.02 g, yield: 78%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 1.32 (6 H, d, J = 6.0 Hz), 2.52 - 2.62 (2 H, m), 2.70 - 2.81 (2 H, m), 4.09 (2 H, q, J = 7.2 Hz), 4.41 - 4.56 (1 H, m), 6.63 (1 H, d, J = 2.6 Hz), 6.76 (1 H, dd, J = 8.5, 2.6 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.27 (1 H, dd, J = 2.1, 0.9 Hz).

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Reference Example 137

To a mixture of ethyl (2E)-3-[2-(benzyloxy)-4-hydroxyphenyl]acrylate (2.5 g), 2-methoxyethanol (1.0 ml), tributylphosphine (3.5 ml) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (4.2 g) at room temperature, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:5, v/v) to give ethyl (2E)-3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]acrylate as a colorless oil (2.5 g, yield: 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.31 (3 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.69 - 3.78 (2 H, m), 4.06 - 4.15 (2 H, m), 4.23 (2 H, q, J = 7.2 Hz), 5.13 (2 H, s), 6.37 - 6.58 (3 H, m), 7.28 - 7.51 (6 H, m), 7.99 (1 H, d, J = 16.2 Hz).

Reference Example 138

To ethyl (2E)-3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.5 g) in a tetrahydrofuran-ethanol mixed solution (1:1, v/v, 100 ml) was added 10% palladium-carbon (0.25 g), and the mixture was stirred under a hydrogen atmosphere for 3 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5 - 1:3, v/v) to give ethyl 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]propanoate as a colorless oil (2.8 g, yield: 95%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.23 (3 H, t, J = 7.2 Hz), 2.62 - 2.70 (2 H, m), 2.78 - 2.86 (2 H, m), 3.44 (3 H, s), 3.70 - 3.75 (2 H, m), 4.04 - 4.09 (2 H, m), 4.14 (2 H, q, J = 7.2 Hz), 6.42 - 6.52 (2 H, m), 6.95 (1 H, d, J = 8.1 Hz), 7.42 - 7.50 (1 H, m).

Reference Example 139

To a solution (40 ml) of ethyl 3-[2-hydroxy-4-(2-

methoxyethoxy)phenyl]propanoate (1.6 g) in N,N-dimethylformamide was added sodium hydride (60% in oil, 285 mg) at room temperature, and the mixture was stirred for 30 min. 2,3-Dichloro-5-(trifluoromethyl)pyridine (0.9 ml) was added to this reaction mixture, and the mixture was stirred at room temperature for 30 min. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanoate as a colorless oil (2.2 g, yield: 84%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 2.50 - 2.63 (2 H, m), 2.72 - 2.84 (2 H, m), 3.43 (3 H, s), 3.65 - 3.79 (2 H, m), 4.02 - 4.16 (4 H, m),6.68 (1 H, d, J = 2.6 Hz), 6.82 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.21 - 8.29 (1 H, m).

Reference Example 140

To a solution (100 ml) of ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanoate (2.2 g) in tetrahydrofuran was added lithium aluminum hydride (186 mg) at room temperature, and the mixture was stirred for 15 min. Sodium sulfate 10 hydrate (1.6 g) was added to this reaction mixture, and the mixture was filtered through celite and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol as a colorless oil (1.7 g, yield: 83%). Recrystallization from ethyl acetate-hexane gave colorless prism crystals. melting point 70°C-71°C.

Reference Example 141

To a solution of ethyl 3-(3-isopropoxy-1H-pyrazol-5-

yl)propionate (1.50 g) in N,N-dimethylformamide (20 ml) was added sodium hydride (60% in oil, 290 mg) at room temperature, and the mixture was stirred for 10 min. 2,4-Difluorobenzylbromide (1.65 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:49 - 1:3, v/v) to give ethyl 3-[1-(2,4-difluorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propionate (660 mg, yield: 28%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (3 H, t, J = 7.2 Hz), 1.32 (6 H, d, J = 6.3 Hz), 2.52 - 2.62 (2 H, m), 2.77 - 2.87 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.60 - 4.76 (1 H, m), 5.13 (2 H, s), 5.47 (1 H, s), 6.66 - 6.97 (3 H, m).

Reference Example 142

A mixture of methyl 3-isopropoxy-1H-pyrazole-5-carboxylate (11.08 g), 2,4-dichlorobenzyl chloride (13.0 g), potassium carbonate (10.00 g) and N,N-dimethylformamide (80 ml) was stirred overnight at room temperature. Water (100 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:8 - 1:2, v/v) to give methyl 1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazole-5-carboxylate (Reference Example 142a) (13.68 g, yield: 66%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.34 (6 H, d, J = 5.8 Hz), 3.81 (3 H, s), 4.72 (1 H, septet, J = 6.2 Hz), 5.67 (2 H, s), 6.28 (1 H, s), 6.54 (1 H, d, J = 8.4 Hz), 7.12 (1 H, dd, J = 8.4, 1.8 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Then, methyl 1-(2,4-dichlorobenzyl)-5-isopropoxy-1H-

pyrazole-3-carboxylate (Reference Example 142b) (6.00 g, yield: 29%) was obtained as colorless crystals. melting point 89-90°C.

Reference Example 143

A solution of methyl 1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazole-5-carboxylate (13.68 g) in tetrahydrofuran (40 ml) was added to a suspension of lithium aluminum hydride (1.90 g) in tetrahydrofuran (70 ml) under ice-cooling over 45 min, and the mixture was stirred for 30 min. Ethanol (20 ml) and then a saturated aqueous ammonium chloride solution (7.0 ml) were added to the reaction mixture, the precipitated inorganic product was filtered off, and washed with acetone. Ethyl acetate (100 ml) was added to the residue, and the mixture was dried ($MgSO_4$), filtrated and concentrated to give [1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]methanol as colorless crystals (12.05 g, yield: 96%). melting point 89-90°C.

Reference Example 144

A solution of dimethyl sulfoxide (10.8 ml) in dichloromethane (100 ml) was cooled to -70°C, oxalyl chloride (6.70 ml) was added over 20 min, and the mixture was stirred for 20 min. Then a solution of [1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]methanol (12.05 g) in dichloromethane (15 ml) was added over 20 min, and the mixture was stirred for 30 min. Triethylamine (29 ml) was added to the reaction mixture over 10 min, and the mixture was gradually warmed to room temperature. 1N Hydrochloric acid (100 ml) was added to the reaction mixture, the dichloromethane layer was separated and concentrated to give a residue. Separately, the aqueous layer was extracted with ethyl acetate (100 ml) and combined with the residue obtained earlier. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:6, v/v) to give 1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazole-

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5-carbaldehyde as a yellow oil (11.37 g, yield: 95%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.35 (6 H, d, J = 6.2 Hz), 4.76 (1 H, septet, J = 6.1 Hz), 5.64 (2 H, s), 6.31 (1 H, s), 6.60 (1 H, d, J = 8.4 Hz), 7.13 (1 H, dd, J = 8.4, 2.2 Hz), 7.39 (1 H, d, J = 2.2 Hz), 9.74 (1 H, s).

Reference Example 145

A solution of 1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazole-5-carbaldehyde (11.37 g) and ethyl diethylphosphonoacetate (8.95 g) in tetrahydrofuran (40 ml) was added to a suspension of sodium hydride (60% in oil, 1.75 g) in N,N-dimethylformamide (140 ml) under ice-cooling over 40 min, and the mixture was stirred at room temperature for 30 min. Water (200 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 ml x2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:6, v/v) to give ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propenoate as a yellow oil (12.78 g, yield: 92%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.30 (3 H, t, J = 6.9 Hz), 1.34 (6 H, d, J = 6.2 Hz), 4.23 (2 H, q, J = 7.2 Hz), 4.72 (1 H, septet, J = 6.4 Hz), 5.33 (2 H, s), 6.00 (1 H, s), 6.27 (1 H, d, J = 15.9 Hz), 6.66 (1 H, d, J = 8.4 Hz), 7.15 (1 H, dd, J = 8.2, 1.8 Hz), 7.35 - 7.45 (2 H, m).

Reference Example 146

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propenoate (12.78 g), 5% palladium-carbon (1.0 g) and tetrahydrofuran (80 ml) was stirred at room temperature under a hydrogen atmosphere for 6 hr. The catalyst was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:6, v/v) to give ethyl 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propionate as a pale-yellow oil (11.37 g, yield: 89%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (3 H, t, J = 7.2 Hz), 1.33 (6 H, d, J = 6.2 Hz), 2.47 - 2.64 (2 H, m), 2.69 - 2.85 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.63 - 4.80 (1 H, m), 5.18 (2 H, s), 5.52 (1 H, s), 6.56 (1 H, d, J = 8.5 Hz), 7.15 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.1 Hz).

Reference Example 147

A mixture of ethyl 3-(3-isopropyl-1H-pyrazol-5-yl)propionate (1.22 g), 2,4-dichlorobenzyl chloride (0.82 ml), potassium carbonate (0.75 g) and N,N-dimethylformamide (10 ml) was stirred overnight at 80°C. Water (15 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (20 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:7, v/v) to give ethyl 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propionate as a yellow oil (1.12 g, yield: 54%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (3 H, t, J = 7.1 Hz), 1.33 (6 H, d, J = 5.8 Hz), 2.50 - 2.63 (2 H, m), 2.70 - 2.82 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.70 (1 H, septet, J = 6.2 Hz), 5.18 (2 H, s), 5.52 (1 H, s), 6.56 (1 H, d, J = 8.0 Hz), 7.15 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Reference Example 148

To a 1N solution of borane in tetrahydrofuran (30 ml) was added 2-chloro-4-trifluoromethylbenzoic acid (2.50 g), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with an aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:4, v/v) to give 2-chloro-4-trifluoromethylbenzyl alcohol (2.23 g, yield: 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:4.85 (2 H, d, J = 9.0 Hz), 7.52 -

7.80 (3 H, m).

Reference Example 149

To a solution of 2-chloro-4-trifluoromethylbenzyl alcohol (2.23 g) and triphenylphosphine (4.17 g) in tetrahydrofuran (25 ml) was added carbon tetrabromide (5.27 g), and the mixture was stirred at room temperature for 2 hr. The reaction solution was concentrated, hexane and diethyl ether was added to the residue, and the insoluble material was filtered off. The mother liquor was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (0:1 - 1:4, v/v) to give 2-chloro-4-trifluoromethylbenzylbromide (2.90 g, yield: 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:4.59 (2 H, s), 7.46 - 7.60 (2 H, m), 7.65 (1 H, s).

Reference Example 150

To a solution of ethyl 3-(3-isopropoxy-1H-pyrazol-5-yl)propionate (1.50 g) in N,N-dimethylformamide (20 ml) was added sodium hydride (60% in oil, 290 mg) at room temperature, and the mixture was stirred for 10 min. 2-Chloro-4-trifluoromethylbenzylbromide (2.17 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:49 - 1:4, v/v) to give ethyl 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}propionate (610 mg, yield: 22%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.23 (3 H, t, J = 7.2 Hz), 1.32 (6 H, d, J = 6.3 Hz), 2.53 - 2.62 (2 H, m), 2.73 - 2.80 (2 H, m), 4.11 (2 H, q, J = 7.2 Hz), 4.64 - 4.76 (1 H, m), 5.25 (2 H, s), 5.54 (1 H, s), 6.69 (1 H, d, J = 7.8 Hz), 7.41 (1 H, d, J = 7.8 Hz), 7.62 (1 H, s).

Reference Example 151

To a mixture of potassium tert-butoxide (55.1 g) in tetrahydrofuran (300 ml) was added a mixture of 3-methylbutan-2-one (30.0 g) and diethyl oxalate (51.0 g) at room temperature over 1 hr. The mixture was stirred overnight at room temperature, acetic acid (47.7 ml) and hydrazine monohydrate (19.0 g) were added, and the mixture was stirred with heating under reflux for 2 hr. The reaction mixture was concentrated, water (200 ml) was added, and the mixture was extracted with ethyl acetate (150 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give ethyl 3-isopropyl-1H-pyrazole-5-carboxylate as a brown oil (31.82 g, yield: 50%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.30 (6 H, d, J = 7.0 Hz), 1.38 (3 H, t, J = 7.2 Hz), 3.04 (1 H, septet, J = 6.8 Hz), 4.37 (2 H, q, J = 6.8 Hz), 4.37 (2 H, q, J = 7.1 Hz), 6.63 (1 H, d, J = 0.6 Hz).

Reference Example 152

Ethyl 3-isopropyl-1H-pyrazole-5-carboxylate (10.00 g), 2,4-dichlorobenzyl chloride (11.8 g), potassium carbonate (9.0 g) and N,N-dimethylformamide (50 ml) were stirred overnight at room temperature. Water (80 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:15 - 1:4, v/v) to give ethyl 1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazole-5-carboxylate (Reference Example 152a) as a brown oil (10.52 g, yield: 56%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (6 H, d, J = 6.8 Hz), 1.29 (3 H, t, J = 7.1 Hz), 3.02 (1 H, septet, J = 6.9 Hz), 4.26 (2 H, q, J = 7.1 Hz), 5.77 (2 H, s), 6.34 (1 H, d, J = 8.6 Hz), 6.78 (1 H, s), 7.09 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.2

Hz).

Then, ethyl 1-(2,4-dichlorobenzyl)-5-isopropyl-1H-pyrazole-3-carboxylate (Reference Example 152b) (8.73 g, yield: 47%) was obtained.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.18 (6 H, d, J = 7.0 Hz), 1.40 (3 H, t, J = 7.1 Hz), 2.79 (1 H, septet, J = 6.8 Hz), 4.42 (2 H, q, J = 7.2 Hz), 5.46 (2 H, s), 6.49 (1 H, d, J = 8.0 Hz), 6.70 (1 H, s), 7.13 (1 H, dd, J = 8.4, 2.2 Hz), 7.40 (1 H, d, J = 1.8 Hz).

Reference Example 153

To a solution of ethyl 1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazole-5-carboxylate (10.52 g) in tetrahydrofuran (100 ml) was added a 1.5 M solution (51.5 ml) of diisobutylaluminum hydride in toluene over 30 min under ice-cooling. The mixture was stirred at room temperature for 30 min, and ethanol (30 ml) and then a saturated aqueous ammonium chloride solution (13 ml) were added to the reaction solution. The precipitated inorganic substance was filtered off, and washed with acetone. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give [1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]methanol as colorless crystals (7.90 g, yield: 86%). melting point 89-90°C.

Reference Example 154

A solution of dimethyl sulfoxide (7.50 ml) in dichloromethane (100 ml) was cooled to -70°C, oxalyl chloride (4.60 ml) was added over 15 min, and the mixture was stirred for 15 min. Then, a solution of [1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]methanol (7.90 g) in dichloromethane (25 ml) was added over 20 min, and the mixture was stirred for 20 min. Triethylamine (20.0 ml) was added to the reaction mixture over 10 min, and the mixture was slowly warmed to room temperature. The reaction mixture was concentrated, and the precipitated salt was filtered off, and washed with

diisopropyl ether. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:15 - 1:6, v/v) to give 1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazole-5-carbaldehyde as a yellow oil (7.08 g, yield: 90%). ^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.30 (6 H, d, J = 7.0 Hz), 3.05 (1 H, septet, J = 6.9 Hz), 5.75 (2 H, s), 6.42 (1 H, d, J = 8.6 Hz), 6.81 (1 H, s), 7.10 (1 H, dd, J = 8.2, 2.0 Hz), 7.39 (1 H, d, J = 2.2 Hz), 9.79 (1 H, s).

Reference Example 155

A solution of 1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazole-5-carbaldehyde (7.08 g) and ethyl diethylphosphonoacetate (5.87 g) in tetrahydrofuran (15 ml) was added to a suspension of sodium hydride (60% in oil, 1.15 g) in N,N-dimethylformamide (40 ml) under ice-cooling over 20 min, and the mixture was stirred at room temperature for 1 hr. Water (80 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (40 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]propenoate as a yellow oil (7.07 g, yield: 81%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 - 1.37 (9 H, m), 2.99 (1 H, septet, J = 6.9 Hz), 4.22 (2 H, q, J = 7.2 Hz), 5.44 (2 H, s), 6.30 (1 H, d, J = 15.8 Hz), 6.44 - 6.53 (2 H, m), 7.13 (1 H, dd, J = 8.2, 2.0 Hz), 7.40 (1 H, d, J = 2.2 Hz), 7.41 (1 H, d, J = 15.8 Hz).

Reference Example 156

A mixture of ethyl (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]propenoate (7.07 g), 5% palladium-carbon (1.4 g) and tetrahydrofuran (45 ml) was stirred at room temperature under a hydrogen atmosphere for 4 hr. The catalyst was filtered off, and the filtrate was concentrated. The

residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:6, v/v) to give ethyl 3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]propionate as a colorless oil (5.36 g, yield: 76%).

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.20 - 1.32 (9 H, m), 2.53 - 2.65 (2 H, m), 2.72 - 2.85 (2 H, m), 2.96 (1 H, septet, J = 7.0 Hz), 4.13 (2 H, q, J = 7.2 Hz), 5.30 (2 H, s), 5.94 (1 H, s), 6.38 (1 H, d, J = 8.4 Hz), 7.13 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Reference Example 157

To a solution of ethyl 3-isopropyl-1H-pyrazole-5-carboxylate (4.39 g) and 2-chloro-4-trifluorobenzyl chloride (6.07 g) in N,N-dimethylformamide (70 ml) was added potassium carbonate (3.99 g), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:49 - 1:4, v/v) to give ethyl 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazole-5-carboxylate (3.80 g, yield: 42%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.1 Hz), 1.30 (6 H, d, J = 7.0 Hz), 2.91 - 3.10 (1 H, m), 4.26 (2 H, q, J = 7.1 Hz), 5.85 (2 H, s), 6.48 (1 H, d, J = 8.1 Hz), 6.80 (1 H, s), 7.38 (1 H, d, J = 8.1 Hz), 7.64 (1 H, s).

Reference Example 158

To a solution of ethyl 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazole-5-carboxylate (3.80 g) in tetrahydrofuran (50 ml) was added a 1.5 M solution (17 ml) of diisobutylaluminum hydride in toluene at 0°C. After stirring at room temperature for 1 hr, methanol was added to quench the reaction. A 10% Rochelle salt aqueous solution (200 ml) was added, and the mixture was stirred for 4 hr and extracted with diethyl ether. The extract was washed with

saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give {1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}methanol (3.37 g, yield: 99%) as a pale-yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (6 H, d, J = 6.9 Hz), 1.63 (1 H, t, J = 5.6 Hz), 2.92 - 3.06 (1 H, m), 4.57 (1 H, d, J = 5.6 Hz), 5.49 (2 H, s), 6.14 (1 H, s), 6.59 (1 H, d, J = 8.0 Hz), 7.39 (1 H, dd, J = 1.2, 8.0 Hz), 7.62 (1 H, d, J = 1.2 Hz).

Reference Example 159

Under a nitrogen atmosphere, to a solution of oxalyl chloride (2.56 g) in methylene chloride (50 ml) was added dimethyl sulfoxide (2.15 ml) at -78°C. After stirring at -78°C for 5 min, a solution of {1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}methanol (3.37 g) in methylene chloride (35 ml) was added. After stirring at -78°C for 1 hr, triethylamine (5.11 g) was added. The reaction mixture was stirred at room temperature for 1 hr and poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:4, v/v) to give 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazole-5-carbaldehyde (3.32 g, yield: 99%) as a pale-yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.31 (6 H, d, J = 7.2 Hz), 2.98 - 3.13 (1 H, m), 5.82 (2 H, s), 6.52 (1 H, d, J = 8.1 Hz), 6.83 (1 H, s), 7.36 (1 H, dd, J = 1.2, 8.1 Hz), 7.65 (1 H, d, J = 1.2 Hz), 9.79 (1 H, s).

Reference Example 160

Under ice-cooling, to a suspension of sodium hydride (60% in oil, 560 mg) in N,N-dimethylformamide (30 ml) was added a mixed solution of 1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazole-5-carbaldehyde (3.32 g) and ethyl

diethylphosphonoacetate (2.69 g) in tetrahydrofuran (15 ml). After stirring at room temperature for 1.5 hr, the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:49 - 3:17, v/v) to give ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}acrylate (1.18 g, yield: 29%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.28 (6 H, d, J = 6.9 Hz), 1.30 (3 H, t, J = 7.2 Hz), 2.93 - 3.07 (1 H, m), 4.21 (2 H, q, J = 7.2 Hz), 5.51 (2 H, s), 6.31 (1 H, d, J = 15.8 Hz), 6.50 (1 H, s), 6.60 (1 H, d, J = 7.8 Hz), 7.38 (1 H, d, J = 15.8 Hz), 7.40 (1 H, d, J = 7.8 Hz), 7.65 (1 H, s).

Reference Example 161

A mixture of ethyl (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}acrylate (1.18 g), 5% palladium-carbon (290 mg) and tetrahydrofuran (15 ml) was hydrogenated at room temperature under atmospheric pressure. The reaction mixture was filtrated, and the filtrate was concentrated to give ethyl 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}propionate (1.00 g, yield: 84%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.2 Hz), 1.26 (6 H, d, J = 7.2 Hz), 2.57 - 2.64 (2 H, m), 2.74 - 2.81 (2 H, m), 2.89 - 3.02 (1 H, m), 4.11 (2 H, q, J = 7.2 Hz), 5.38 (2 H, s), 5.96 (1 H, s), 6.51 (1 H, d, J = 8.1 Hz), 7.40 (1 H, dd, J = 1.2, 8.1 Hz), 7.63 (1 H, d, J = 1.2 Hz).

Reference Example 162

To a mixture of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (0.98 g), cyclohexanol (0.48 g), tributylphosphine (0.89 g) and tetrahydrofuran (10 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.03 g) at room temperature, and the mixture was stirred for 6 hr.

Tributylphosphine (0.89 g) and 1,1'-(azodicarbonyl)dipiperidine (1.03 g) were added to the reaction mixture at room temperature, and the mixture was stirred at 50°C for 24 hr. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (3:17 - 3:7, v/v) to give ethyl (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]acrylate as a colorless oil (0.80 g, yield: 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.26 - 1.44 (7 H, m), 1.46 - 1.70 (4 H, m), 1.70 - 2.04 (4 H, m), 3.45 (3 H, s), 3.73 - 3.76 (2 H, m), 4.11 - 4.14 (2 H, m), 4.20 - 4.32 (3 H, m), 6.38 - 6.52 (3 H, m), 7.42 (1 H, d, J = 8.7 Hz), 7.93 (1 H, d, J = 16.2 Hz).

Reference Example 163

A mixture of ethyl (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]acrylate (0.80 g), 10% palladium-carbon (0.15 g) and tetrahydrofuran (35 ml) was stirred under a hydrogen atmosphere at room temperature for 3 hr. The catalyst was filtered off, and the filtrate was concentrated to give ethyl 3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propanoate as a pale-black oil (0.80 g, yield: 99%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.23 (3 H, t, J = 7.2 Hz), 1.30 - 1.62 (6 H, m), 1.70 - 1.98 (4 H, m), 2.54 - 2.59 (2 H, m), 2.83 - 2.88 (2 H, m), 3.44 (3 H, s), 3.71 - 3.74 (2 H, m), 4.06 - 4.14 (4 H, m), 4.20 - 4.28 (1 H, m), 6.36 (1 H, dd, J = 8.4, 2.4 Hz), 6.48 (1 H, d, J = 2.4 Hz), 7.01 (1 H, d, J = 8.1 Hz).

Reference Example 164

Ethyl 3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propanoate (0.80 g) was dissolved in tetrahydrofuran (20 ml), a 1.5 M diisobutylaluminum hydride solution in toluene (6.1 ml) was added at 0°C, and the mixture was stirred at room temperature for 1 hr. Sodium sulfate

decahydrate (2.95 g) and diethyl ether (50 ml) were added to the reaction mixture, and the mixture was stirred overnight. The resulting solid was filtered off and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 2:3, v/v) to give 3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propan-1-ol as a colorless oil (0.63 g, yield: 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.24 - 1.42 (2 H, m), 1.44 - 1.60 (4 H, m), 1.72 - 1.84 (4 H, m), 1.96 - 2.00 (3 H, m), 2.66 (2 H, t, J = 6.9 Hz), 3.45 (3 H, s), 3.55 (2 H, q, J = 6.0 Hz), 3.72 - 3.75 (2 H, m), 4.07 - 4.10 (2 H, m), 4.20 - 4.28 (1 H, m), 6.42 (1 H, dd, J = 8.1, 2.4 Hz), 6.52 (1 H, d, J = 2.4 Hz), 7.01 (1 H, d, J = 8.1 Hz).

Reference Example 165

A mixture of ethyl (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylate (1.18 g), 10% palladium-carbon (0.25 g) and tetrahydrofuran (50 ml) was stirred under a hydrogen atmosphere at room temperature for 1 hr. The catalyst was filtered off, and the filtrate was concentrated to give ethyl 3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propanoate as a colorless oil (1.18 g, yield: 98%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.32 - 0.34 (2 H, m), 0.59 - 0.62 (2 H, m), 1.21 - 1.30 (4 H, m), 2.56 - 2.62 (2 H, m), 2.89 (2 H, t, J = 7.8 Hz), 3.44 (3 H, s), 3.71 - 3.74 (2 H, m), 3.78 (2 H, d, J = 6.6 Hz), 4.07 - 4.15 (4 H, m), 6.39 (1 H, dd, J = 8.1, 2.4 Hz), 6.45 (1 H, d, J = 2.4 Hz), 7.02 (1 H, d, J = 8.1 Hz).

Reference Example 166

Ethyl 3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propanoate (1.18 g) was dissolved in tetrahydrofuran (30 ml), a 1.5 M diisobutylaluminum hydride solution in toluene (10 ml) was added at 0°C, and the mixture was stirred at room temperature for 40 min. Sodium sulfate

decahydrate (4.83 g) and diethyl ether (60 ml) were added to the reaction mixture, and the mixture was stirred overnight. The resulting solid was filtered off and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 9:11, v/v) to give 3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propan-1-ol as a colorless oil (0.99 g, yield: 94%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.32 - 0.38 (2 H, m), 0.60 - 0.66 (2 H, m), 1.22 - 1.32 (1 H, m), 1.76 - 1.84 (2 H, m), 2.14 (1 H, t, J = 6.3 Hz), 2.70 (2 H, t, J = 6.6 Hz), 3.44 (3 H, s), 3.55 (2 H, q, J = 6.0 Hz), 3.71 - 3.75 (2 H, m), 3.78 (2 H, d, J = 6.9 Hz), 4.07 - 4.10 (2 H, m), 6.42 - 6.46 (2 H, m), 7.01 (1 H, d, J = 8.1 Hz).

Reference Example 167

A mixture of ethyl (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylate (1.05 g), 10% palladium-carbon (0.20 g) and tetrahydrofuran (40 ml) was stirred under a hydrogen atmosphere at room temperature for 1 hr. The catalyst was filtered off, and the filtrate was concentrated to give ethyl 3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propanoate as a colorless oil (1.18 g, yield: 98%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.20 - 1.25 (3 H, m), 1.80 - 2.12 (4 H, m), 2.53 - 2.59 (2 H, m), 2.84 - 2.90 (2 H, m), 3.39 (3 H, s), 3.71 - 3.74 (2 H, m), 3.79 - 3.85 (1 H, m), 3.86 - 4.00 (3 H, m), 4.06 - 4.14 (4 H, m), 4.23 - 4.30 (1 H, m), 6.40 (1 H, dd, J = 8.1, 2.4 Hz), 6.48 (1 H, d, J = 2.4 Hz), 7.02 (1 H, d, J = 8.4 Hz).

Reference Example 168

3-[4-(2-Methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propanoate (1.04 g) was dissolved in tetrahydrofuran (24 ml), a 1.5 M diisobutylaluminum hydride solution in toluene (8.0 ml) was added at 0°C, and the mixture was stirred at room temperature for 20 min. Sodium sulfate

decahydrate (3.87 g) and diethyl ether (70 ml) were added to the reaction mixture, and the mixture was stirred overnight. The resulting solid was filtered off and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 1:1, v/v) to give 3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propan-1-ol as a colorless oil (0.50 g, yield: 54%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.66 - 2.12 (6 H, m), 2.58 - 2.67 (2 H, m), 2.72 - 2.82 (1 H, m), 3.44 (3 H, s), 3.51 (2 H, q, J = 5.7 Hz), 3.72 - 3.75 (2 H, m), 3.80 - 4.00 (4 H, m), 4.07 - 4.11 (2 H, m), 4.24 - 4.32 (1 H, m), 6.43 - 6.48 (2 H, m), 7.02 (1 H, d, J = 8.4 Hz).

Reference Example 169

To a solution (400 ml) of 2,4-dihydroxybenzaldehyde (30.0 g), 2-methoxyethanol (21.4 g) and triphenylphosphine (74.0 g) in toluene was added dropwise a 40% diethyl azodicarboxylate toluene solution (128 ml) at 0°C over about 25 min, and the mixture was warmed to room temperature and stirred for 90 min. The reaction mixture was concentrated, and the residue was mixed with ethyl acetate, the insoluble material was filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:5 - 1:2, v/v) to give 2-hydroxy-4-(2-methoxyethoxy)benzaldehyde (14.7 g, yield: 34%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.45 (3 H, s), 3.74 - 3.78 (2 H, m), 4.15 - 4.18 (2 H, m), 6.44 (1 H, d, J = 2.4 Hz), 6.57 (1 H, dd, J = 8.7, 2.4 Hz), 7.42 (1 H, d, J = 8.7 Hz), 9.71 (1 H, s), 11.46 (1 H, s).

Reference Example 170

To a solution (200 ml) of 2-hydroxy-4-(2-methoxyethoxy)benzaldehyde (11.4 g) in tetrahydrofuran was added [(ethoxycarbonyl)methylene]triphenyl phosphorane (22.2 g) at 0°C, and the mixture was warmed to room temperature and

stirred for 4 hr. The reaction mixture was concentrated, and the residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (2:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (15.7 g, yield: 82%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.33 (3 H, t, J = 7.2 Hz), 3.47 (3 H, s), 3.76 - 3.78 (2 H, m), 4.10 - 4.13 (2 H, m), 4.26 (2 H, q, J = 7.2 Hz), 6.44 - 6.52 (3 H, m), 7.09 (1 H, s), 7.37 (1 H, d, J = 9.3 Hz), 7.92 (1 H, d, J = 16.2 Hz).

Reference Example 171

To a mixed solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (2.00 g) in acetonitrile (20 ml) and N,N-dimethylformamide (10 ml) were added bromomethylcyclohexane (4.04 g), potassium carbonate (3.10 g) and sodium iodide (2.37 g), and the mixture was heated under reflux for 40 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.22 g, yield: 81%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.07 - 1.38 (8 H, m), 1.75 - 1.90 (6 H, m), 3.45 (3 H, s), 3.75 - 3.79 (4 H, m), 4.12 - 4.15 (2 H, m), 4.24 (2 H, q, J = 7.2 Hz), 6.40 - 6.49 (3 H, m), 7.43 (1 H, d, J = 9.3 Hz), 7.93 (1 H, d, J = 15.9 Hz).

Reference Example 172

To a mixed solution of ethyl (2E)-3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.21 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (12 ml), and the mixture was stirred at 60°C for 3 hr. After cooling, the reaction

mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (1.91 g, yield: 93%) as colorless crystals. melting point 111.5-112.5°C.

Reference Example 173

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (2.00 g) in N,N-dimethylformamide (10 ml) were added (bromomethyl)cyclopropane (1.57 g) and potassium carbonate (2.07 g), and the mixture was stirred at room temperature for 20 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.03 g, yield: 84%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.33 - 0.38 (2 H, m), 0.63 - 0.69 (2 H, m), 1.29 - 1.36 (4 H, m), 3.45 (3 H, s), 3.72 - 3.76 (2 H, m), 3.83 (2 H, d, J = 6.9 Hz), 4.09 - 4.13 (2 H, m), 4.24 (2 H, q, J = 7.2 Hz), 6.45 - 6.51 (3 H, m), 7.43 (1 H, d, J = 8.4 Hz), 7.94 (1 H, d, J = 16.2 Hz).

Reference Example 174

To a mixed solution of ethyl (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.02 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (13 ml), and the mixture was stirred at 60°C for 2 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained

mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (1.85 g, yield: 99%) as colorless crystals. melting point 117.8-118.8°C.

Reference Example 175

To a mixed solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (2.00 g), 1-Boc-4-hydroxypiperidine (2.30 g) and tributylphosphine (4.58 g) in toluene (260 ml) and tetrahydrofuran (10 ml) was slowly added 1,1'-(azodicarbonyl)dipiperidine (5.28 g) at room temperature, and the mixture was stirred at room temperature for 30 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, water was further poured thereinto, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. An ethyl acetate-hexane (1:1, v/v) mixed solvent was added to the obtained residue, and the insoluble material was filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (2:3, v/v) to give tert-butyl 4-[2-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]-5-(2-methoxyethoxy)phenoxy]piperidine-1-carboxylate (2.54 g, yield: 75%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.32 (3 H, t, J = 7.2 Hz), 1.47 (9 H, s), 1.76 - 1.86 (2 H, m), 1.87 - 1.99 (2 H, m), 3.37 - 3.50 (5 H, m), 3.64 - 3.76 (4 H, m), 4.12 - 4.14 (2 H, m), 4.24 (2 H, q, J = 7.2 Hz), 4.48 - 4.52 (1 H, m), 6.39 (1 H, d, J = 16.2 Hz), 6.50 - 6.52 (2 H, m), 7.44 - 7.47 (1 H, m), 7.91 (1 H, d, J = 16.2 Hz).

Reference Example 176

To a mixed solution of tert-butyl 4-[2-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]-5-(2-methoxyethoxy)phenoxy]piperidine-1-

carboxylate (2.54 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (11.3 ml), and the mixture was stirred at 60°C for 90 min. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated to give (2E)-3-[2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (2.28 g, yield: 95%) as a pale-yellow amorphous solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40 (9 H, s), 1.55 - 1.61 (2 H, m), 1.85 - 1.95 (2 H, m), 3.20 - 3.31 (5 H, m), 3.57 - 3.65 (4 H, m), 4.12 - 4.15 (2 H, m), 4.69 - 4.76 (1 H, m), 6.38 (1 H, d, J = 16.2 Hz), 6.57 (1 H, dd, J = 8.4, 2.1 Hz), 6.71 (1 H, d, J = 2.1 Hz), 7.61 (1 H, d, J = 8.4 Hz), 7.75 (1 H, d, J = 16.2 Hz), 12.09 (1 H, brs).

Reference Example 177

To a mixed solution of ethyl (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.07 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (12 ml), and the mixture was stirred at 60°C for 90 min. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (1.59 g, yield: 83%) as colorless crystals. melting point 102.0-113.6°C.

Reference Example 178

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (2.70 g) in N,N-dimethylformamide (22 ml) were added tetrahydrofurfuryl

bromide (8.58 g), sodium iodide (7.56 g) and potassium carbonate (6.97 g), and the mixture was stirred at 80°C for 170 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylate (2.65 g, yield: 75%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.31 (3 H, t, J = 7.2 Hz), 1.80 - 2.14 (4 H, m), 3.45 (3 H, s), 3.73 - 3.76 (2 H, m), 3.82 - 3.88 (1 H, m), 3.90 - 4.08 (3 H, m), 4.12 - 4.14 (2 H, m), 4.23 (2 H, q, J = 7.2 Hz), 4.30 - 4.35 (1 H, m), 6.42 (1 H, d, J = 16.2 Hz), 6.50 - 6.52 (2 H, m), 7.42 (1 H, d, J = 9.0 Hz), 7.91 (1 H, d, J = 16.2 Hz).

Reference Example 179

To a mixed solution of ethyl (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylate (2.65 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (15 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated and neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylic acid as colorless crystals (1.99 g, yield: 81%). melting point 106.1-107.7°C.

Reference Example 180

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (1.40 g) in N,N-dimethylformamide (15 ml) were added 2,4-dichlorobenzyl chloride (1.59 g) and potassium carbonate (1.45 g), and the

mixture was stirred at room temperature for 60 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (2.07 g, yield: 92%) as colorless crystals. melting point 100.8-101.1°C.

Reference Example 181

To a mixed solution of ethyl (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.95 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (9 ml), and the mixture was stirred at 60°C for 90 min. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from diisopropyl ether-methanol to give (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (1.80 g, yield: 99%) as colorless crystals. melting point 175.6-177.5°C.

Reference Example 182

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (900 mg) in N,N-dimethylformamide (15 ml) was added sodium hydride (60% in oil, 188 mg), and the mixture was stirred at room temperature for 1 hr. 2,3,5-Trichloropyridine (925 mg) was added to the reaction mixture, and the mixture was stirred at 80°C for 36 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica

gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give ethyl (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.01 g, yield: 72%) as colorless crystals. melting point 70.7-71.3°C.

Reference Example 183

To a mixed solution of ethyl (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.45 g) in tetrahydrofuran (15 ml) and ethanol (15 ml) was added a 1N aqueous sodium hydroxide solution (7 ml), and the mixture was stirred at 60°C for 1 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from tetrahydrofuran-hexane to give (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (1.24 g, yield: 92%) as colorless crystals. melting point 182.3-184.0°C.

Reference Example 184

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (1.20 g) in N,N-dimethylformamide (15 ml) were added 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (1.03 g) and potassium carbonate (1.24 g), and the mixture was stirred at room temperature for 40 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-

yl)methoxy]phenyl}acrylate (1.85 g, yield: 94%) as colorless crystals. melting point 109.4-110.0°C.

Reference Example 185

To a mixed solution of ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}acrylate (1.73 g) in tetrahydrofuran (15 ml) and ethanol (15 ml) was added a 1N aqueous sodium hydroxide solution (12 ml), and the mixture was stirred at 60°C for 6 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from tetrahydrofuran-hexane to give (2E)-3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}acrylic acid (1.56 g, yield: 96%) as colorless crystals. melting point 194.3-195.8°C.

Reference Example 186

To a mixed solution of ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[2-nitro-5-(trifluoromethyl)phenoxy]phenyl}acrylate (1.01 g) in tetrahydrofuran (5 ml) and ethanol (5 ml) was added a 1N aqueous sodium hydroxide solution (5 ml), and the mixture was stirred at 70°C for 2 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-3-{4-(2-methoxyethoxy)-2-[2-nitro-5-(trifluoromethyl)phenoxy]phenyl}acrylic acid (0.58 g, yield: 61%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.25 (3 H, s), 3.57 - 3.62 (2 H, m), 4.04 - 4.11 (2 H, m), 6.38 - 6.92 (3 H, m), 7.46 - 7.90 (4 H, m), 8.32 - 8.35 (1 H, m), 12.09 (1 H, brs).

Reference Example 187

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (1.19 g) in N,N-dimethylformamide (8 ml) were added 3-chloro-4-fluorobenzotrifluoride (1.06 g) and potassium carbonate (1.23 g), and the mixture was stirred at 80°C for 55 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v) to give ethyl (2E)-3-[2-[2-chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.76 g, yield: 88%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.2 Hz), 3.41 (3 H, s), 3.69 - 3.72 (2 H, m), 4.05 - 4.09 (2 H, m), 4.22 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 2.4 Hz), 6.43 (1 H, d, J = 16.2 Hz), 6.77 (1 H, dd, J = 8.7, 2.4 Hz), 6.96 (1 H, d, J = 8.7 Hz), 7.45 (1 H, d, J = 8.7 Hz), 7.59 (1 H, d, J = 8.7 Hz), 7.75 (1 H, s), 7.85 (1 H, d, J = 16.2 Hz).

Reference Example 188

To a mixed solution of ethyl (2E)-3-[2-[2-chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.76 g) in tetrahydrofuran (8 ml) and ethanol (8 ml) was added a 1N aqueous sodium hydroxide solution (8 ml), and the mixture was stirred at 50°C for 90 min. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[2-chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (1.60 g, yield: 97%) as colorless crystals. melting point 165.6-166.0°C.

Reference Example 189

To a solution of ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[(trifluoromethyl)sulfonyl]oxy}phenyl)acrylate (1.50 g) in tetrahydrofuran (20 ml) were added 4-aminobenzotrifluoride (948 mg), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (282 mg), palladium acetate (67 mg) and cesium carbonate (1.83 g), and the mixture was heated under reflux for 16 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)acrylate (1.00 g, yield: 65%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.1 Hz), 3.43 (3 H, s), 3.73 - 3.77 (2 H, m), 4.07 - 4.10 (2 H, m), 4.23 (2 H, q, J = 7.1 Hz), 5.85 (1 H, s), 6.31 (1 H, d, J = 15.7 Hz), 6.69 - 6.73 (1 H, m), 6.88 (1 H, d, J = 2.4 Hz), 6.98 (2 H, d, J = 8.7 Hz), 7.47 - 7.56 (3 H, m), 7.82 (1 H, d, J = 15.7 Hz).

Reference Example 190

To a mixed solution of ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)acrylate (1.42 g) in tetrahydrofuran (8 ml) and ethanol (8 ml) was added a 1N aqueous sodium hydroxide solution (7 ml), and the mixture was stirred at 50°C for 2 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)acrylic acid (0.96 g, yield: 72%) as yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.29 (3 H, s), 3.62 - 3.65 (2 H, m), 4.05 - 4.16 (2 H, m), 6.33 - 6.43 (2 H, m), 6.77 - 6.98 (3

H, m), 7.48 - 7.80 (4 H, m), 8.60 (1 H, s), 12.12 (1 H, s).

Reference Example 191

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (1.48 g) in N,N-dimethylformamide (10 ml) were added 2,5-dibromothiazole (1.61 g) and potassium carbonate (1.53 g), and the mixture was stirred at 80°C for 22 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give ethyl (2E)-3-[2-[(5-bromo-1,3-thiazol-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.69 g, yield: 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.31 (3 H, t, J = 7.2 Hz), 3.43 (3 H, s), 3.73 - 3.75 (2 H, m), 4.10 - 4.14 (2 H, m), 4.23 (2 H, q, J = 7.2 Hz), 6.37 (1 H, d, J = 16.1 Hz), 6.83 (1 H, s), 6.87 (1 H, d, J = 8.7 Hz), 7.16 (1 H, s), 7.60 (1 H, d, J = 8.7 Hz), 7.79 (1 H, d, J = 16.1 Hz).

Reference Example 192

To a mixed solution of ethyl (2E)-3-[2-[(5-bromo-1,3-thiazol-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (1.67 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (8 ml), and the mixture was stirred at 50°C for 30 min. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-3-[2-[(5-bromo-1,3-thiazol-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (1.46 g, yield: 93%) as colorless crystals. melting point 144.0-145.1°C.

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Reference Example 193

To a solution of ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[(trifluoromethyl)sulfonyl]oxy}phenyl)acrylate (1.66 g) in tetrahydrofuran (20 ml) were added 2-chloro-4-(trifluoromethyl)aniline (1.89 g), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (519 mg), palladium acetate (140 mg) and cesium carbonate (2.06 g), and the mixture was heated under reflux for 8 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v) to give ethyl (2E)-3-[2-{[2-chloro-4-(trifluoromethyl)phenyl]amino}-4-(2-methoxyethoxy)phenyl]acrylate (1.00 g, yield: 54%) as yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.29 (3 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.73 - 3.79 (2 H, m), 4.16 - 4.27 (4 H, m), 6.23 (1 H, s), 6.34 (1 H, d, J = 15.9 z), 6.55 - 6.59 (1 H, m), 6.85 - 6.91 (2 H, m), 7.32 - 7.62 (3 H, m), 7.77 (1 H, d, J = 15.9 Hz).

Reference Example 194

To a mixed solution of ethyl (2E)-3-[2-{[2-chloro-4-(trifluoromethyl)phenyl]amino}-4-(2-methoxyethoxy)phenyl]acrylate (1.00 g) in tetrahydrofuran (5 ml) and ethanol (5 ml) was added a 1N aqueous sodium hydroxide solution (4.5 ml), and the mixture was stirred at 60°C for 30 min. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-3-[2-{[2-chloro-4-(trifluoromethyl)phenyl]amino}-4-(2-methoxyethoxy)phenyl]acrylic acid (515 mg, yield: 55%) as

colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.29 (3 H, s), 3.62 - 3.65 (2 H, m), 4.10 - 4.13 (2 H, m), 6.39 (1 H, t, J = 16.1 Hz), 6.53 (1 H, d, J = 9.0 Hz), 6.80 (1 H, d, J = 2.4 Hz), 6.89 - 6.93 (1 H, m), 7.38 - 7.42 (1 H, m), 7.54 (1 H, t, J = 16.1 Hz), 7.74 (1 H, d, J = 2.1 Hz), 7.86 (1 H, d, J = 9.0 Hz), 8.18 (1 H, s), 12.19 (1 H, s).

Reference Example 195

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (1.10 g) in N,N-dimethylformamide (10 ml) were added 2-chloro-5-nitro-3-picoline (1.03 g) and potassium carbonate (1.14 g), and the mixture was stirred at 80°C for 2 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-nitropyridin-2-yl)oxy]phenyl}acrylate (1.63 g, yield: 98%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.27 (3 H, t, J = 7.1 Hz), 2.52 (3 H, s), 3.44 (3 H, s), 3.73 - 3.76 (2 H, m), 4.12 - 4.15 (2 H, m), 4.18 (2 H, q, J = 7.1 Hz), 6.32 (1 H, d, J = 16.2 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.90 (1 H, dd, J = 8.7, 2.4 Hz), 7.63 (1 H, d, J = 8.7 Hz), 7.64 (1 H, d, J = 16.2 Hz), 8.35 (1 H, d, J = 1.8 Hz), 8.81 (1 H, d, J = 1.8 Hz).

Reference Example 196

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (1.05 g) in N,N-dimethylformamide (10 ml) were added 3-chloro-6-(trifluoromethyl)pyridazine (1.48 g) and potassium carbonate (1.53 g), and the mixture was stirred at 80°C for 3 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate

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layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-methanol (49:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}phenyl)acrylate (2.14 g, yield: 90%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.27 (3 H, t, J = 7.1 Hz), 3.43 (3 H, s), 3.73 - 3.75 (2 H, m), 4.11 - 4.14 (2 H, m), 4.19 (2 H, q, J = 7.1 Hz), 6.35 (1 H, d, J = 16.2 Hz), 6.75 (1 H, d, J = 2.7 Hz), 6.91 (1 H, dd, J = 8.7, 2.7 Hz), 7.40 (1 H, d, J = 9.0 Hz), 7.64 (1 H, d, J = 8.7 Hz), 7.70 (1 H, d, J = 16.2 Hz), 7.84 (1 H, d, J = 9.0 Hz).

Reference Example 197

To a solution of 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzaldehyde (500 mg) in acetic acid (8 ml) were added methylmalonic acid (859 mg) and pyrrolidine (827 mg), and the mixture was stirred at 100°C for 24 hr. 1N Hydrochloric acid (1 ml) and water (10 ml) were added to the reaction mixture, and the mixture was stirred at room temperature for 20 min. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (455 mg, yield: 78%) as colorless crystals. melting point 126.0-127.0°C.

Reference Example 198

To a solution of triethyl 2-phosphonobutyrate (0.83 g) in tetrahydrofuran (10 ml) was added sodium hydride (60% in oil, 145 mg) at 0°C, and the mixture was stirred at 0°C for 15 min.

To this reaction mixture was added a solution of 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzaldehyde (1.02 g) in tetrahydrofuran (10 ml) at 0°C, and the mixture was warmed to room temperature and stirred for 3 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give ethyl (2E)-2-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzylidene]butanoate (922 mg, yield: 70%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.08 (3 H, t, J = 7.2 Hz), 1.26 (3 H, t, J = 7.2 Hz), 2.45 (2 H, q, J = 7.2 Hz), 3.44 (3 H, s), 3.73 - 3.76 (2 H, m), 4.11 - 4.14 (2 H, m), 4.18 (2 H, q, J = 7.2 Hz), 6.74 (1 H, d, J = 3.0 Hz), 6.86 (1 H, dd, J = 9.0, 3.0 Hz), 7.34 (1 H, d, J = 9.0 Hz), 7.48 (1 H, s), 7.75 (1 H, d, J = 2.1 Hz), 7.91 (1 H, d, J = 2.1 Hz).

Reference Example 199

To a mixed solution of ethyl (2E)-2-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzylidene]butanoate (908 mg) in tetrahydrofuran (5 ml) and ethanol (5 ml) was added a 1N aqueous sodium hydroxide solution (6 ml), and the mixture was stirred at 60°C for 6 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-2-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzylidene]butanoic acid (772 mg, yield: 91%) as colorless crystals. melting point 139.0-139.9°C.

Reference Example 200

To a solution of 4-iodo-3-nitrophenol (5.33 g) in acetone (60 ml) were added 2-bromoethyl methyl ether (11.1 g), sodium iodide (3.65 g) and potassium carbonate (6.98 g), and the mixture was heated under reflux for 20 hr. The reaction mixture was concentrated, water was poured into the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v) to give 1-iodo-4-(2-methoxyethoxy)-2-nitrobenzene (5.59 g, yield: 86%) as pale-yellow crystals.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.44 (3 H, s), 3.76 (2 H, t, J = 4.5 Hz), 4.15 (2 H, t, J = 4.5 Hz), 6.90 (1 H, dd, J = 9.0, 2.7 Hz), 7.46 (1 H, d, J = 2.7 Hz), 7.87 (1 H, d, J = 9.0 Hz).

Reference Example 201

To a solution of 1-iodo-4-(2-methoxyethoxy)-2-nitrobenzene (5.59 g) in acetonitrile (50 ml) were added ethyl acrylate (2.62 g), triethylamine (3.62 g) and palladium acetate (116 mg), and the mixture was heated under reflux for 5 hr. After cooling, the reaction mixture was concentrated, water was poured into the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give ethyl (2E)-3-[4-(2-methoxyethoxy)-2-nitrophenyl]acrylate (4.94 g, yield: 96%) as pale-yellow crystals.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.33 (3 H, t, J = 7.2 Hz), 3.46 (3 H, s), 3.78 (2 H, t, J = 4.5 Hz), 4.21 (2 H, t, J = 4.5 Hz), 4.27 (2 H, q, J = 7.2 Hz), 6.30 (1 H, d, J = 15.9 Hz), 7.21 (1 H, dd, J = 8.7, 2.7 Hz), 7.53 (1 H, d, J = 2.7 Hz), 7.57 (1 H, d, J = 8.7 Hz), 8.03 (1 H, d, J = 15.9 Hz).

Reference Example 202

To a mixture of water (60 ml) and zinc (7.56 g) was added

a solution of (2E)-3-[4-(2-methoxyethoxy)-2-nitrophenyl]acrylate (6.83 g) in acetic acid (60 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, the obtained residue was basified with a 1N aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give ethyl (2E)-3-[2-amino-4-(2-methoxyethoxy)phenyl]acrylate (5.03 g, yield: 82%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.32 (3 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.73 (2 H, t, J = 4.8 Hz), 3.95 (2 H, s), 4.09 (2 H, t, J = 4.8 Hz), 4.24 (2 H, q, J = 7.2 Hz), 6.20 - 6.25 (2 H, m), 6.36 (1 H, m), 7.33 (1 H, d, J = 8.7 Hz), 7.74 (1 H, d, J = 15.6 Hz).

Reference Example 203

To a solution of ethyl (2E)-3-[2-amino-4-(2-methoxyethoxy)phenyl]acrylate (640 mg) in tetrahydrofuran (10 ml) were added 2,4-dichlorobenzoyl chloride (685 mg) and triethylamine (490 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with an aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The obtained crude crystals were recrystallized from ethanol-hexane to give ethyl (2E)-3-[2-[(2,4-dichlorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylate (812 mg, yield: 77%) as colorless crystals. melting point 170.1-170.5°C.

Reference Example 204

To a mixed solution of ethyl (2E)-3-[2-[(2,4-dichlorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylate (472 mg) in tetrahydrofuran (8 ml) and ethanol (8 ml) was added a

1N aqueous sodium hydroxide solution (2.5 ml), and the mixture was stirred at 60°C for 2 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained crude crystals were recrystallized from methanol-diisopropyl ether to give (2E)-3-[2-[(2,4-dichlorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylic acid (422 mg, yield: 96%) as colorless crystals. melting point 242.8-244.8°C.

Reference Example 205

To a solution of 2-hydroxy-4-(methoxymethoxy)benzaldehyde (7.04 g) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 1.88 g), and the mixture was stirred at room temperature for 30 min. 2,3,5-Trichloropyridine (7.40 g) were added to the reaction mixture, and the mixture was stirred at 110°C for 14 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5, v/v) to give 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(methoxymethoxy)benzaldehyde (5.33 g, yield: 42%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.48 (3 H, s), 5.23 (2 H, s), 6.85 (1 H, d, J = 2.4 Hz), 7.03 (1 H, dd, J = 9.0, 2.4 Hz), 7.82 (1 H, d, J = 2.4 Hz), 7.92 (1 H, d, J = 9.0 Hz), 7.95 (1 H, d, J = 2.4 Hz), 10.05 (1 H, s).

Reference Example 206

To a solution of 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(methoxymethoxy)benzaldehyde (4.07 g) in acetone (25 ml) was added 1N hydrochloric acid (25 ml), and the mixture was heated under reflux for 2 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with a 1N

aqueous sodium hydroxide solution. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated to give 2-[(3,5-dichloropyridin-2-yl)oxy]-4-hydroxybenzaldehyde as colorless crystals (3.60 g, yield: 99%).

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.63 (1 H, d, J = 2.4 Hz), 6.85 (1 H, dd, J = 8.4, 2.1 Hz), 7.78 (1 H, d, J = 8.4 Hz), 8.13 (1 H, d, J = 2.4 Hz), 8.37 (1 H, d, J = 2.4 Hz), 9.81 (1 H, s), 10.95 (1 H, s).

Reference Example 207

To a solution of 2-[(3,5-dichloropyridin-2-yl)oxy]-4-hydroxybenzaldehyde (3.60 g) in N,N-dimethylformamide (25 ml) were added 1-bromo-3-methoxypropane (2.89 g), sodium iodide (2.85 g) and potassium carbonate (3.48 g), and the mixture was stirred at 80°C for 2 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v) to give 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(3-methoxypropoxy)benzaldehyde (3.94 g, yield: 87%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.01 - 2.10 (2 H, m), 3.34 (3 H, s), 3.53 (2 H, t, J = 6.0 Hz), 4.11 (2 H, t, J = 6.0 Hz), 6.68 (1 H, d, J = 2.1 Hz), 6.89 (1 H, dd, J = 8.7, 2.1 Hz), 7.82 (1 H, d, J = 2.4 Hz), 7.90 (1 H, d, J = 8.7 Hz), 7.95 (1 H, d, J = 2.4 Hz), 10.03 (1 H, s).

Reference Example 208

To a solution of 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(3-methoxypropoxy)benzaldehyde (745 mg) in acetic acid (12 ml) were added methylmalonic acid (1.24 g) and pyrrolidine (1.18 g), and the mixture was stirred at 100°C for 66 hr. After

cooling, 1N hydrochloric acid (2 ml) and water (10 ml) were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(3-methoxypropoxy)phenyl]-2-methylacrylic acid (658 mg, yield: 76%) as colorless crystals. melting point 128.4-129.5°C.

Reference Example 209

To a solution of (2E)-3-[2-amino-4-(2-methoxyethoxy)phenyl]acrylate (615 mg) in tetrahydrofuran (15 ml) were added 2,4-difluorobenzoyl chloride (490 mg) and triethylamine (480 mg), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, an aqueous sodium hydrogencarbonate solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with an aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), and concentrated. The obtained crude crystals were recrystallized from tetrahydrofuran-hexane to give ethyl (2E)-3-[2-[(2,4-difluorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylate (718 mg, yield: 76%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.33 (3 H, t, J = 7.2 Hz), 3.45 (3 H, s), 3.75 - 3.78 (2 H, m), 4.17 - 4.21 (2 H, m), 4.26 (2 H, q, J = 7.2 Hz), 6.34 (1 H, d, J = 15.6 Hz), 6.84 (1 H, dd, J = 8.7, 2.7 Hz), 6.93 - 7.11 (2 H, m), 7.54 (1 H, d, J = 8.7 Hz), 7.72 (1 H, d, J = 2.7 Hz), 7.85 (1 H, d, J = 15.6 Hz), 8.20 - 8.25 (1 H, m), 8.44 - 8.49 (1 H, m).

Reference Example 210

To a mixed solution of ethyl (2E)-3-[2-[(2,4-difluorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylate (572 mg) in tetrahydrofuran (6 ml) and ethanol (6 ml) was added a

1N aqueous sodium hydroxide solution (3 ml), and the mixture was stirred at 60°C for 2 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from tetrahydrofuran-hexane to give (2E)-3-[2-[(2,4-difluorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylic acid (460 mg, yield: 86%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.31 (3 H, s), 3.65 - 3.68 (2 H, m), 4.12 - 4.15 (2 H, m), 6.37 (1 H, d, J = 15.6 Hz), 6.91 (1 H, dd, J = 8.7, 2.4 Hz), 7.08 (1 H, s), 7.22 - 7.30 (1 H, m), 7.41 - 7.49 (1 H, m), 7.72 (1 H, d, J = 15.6 Hz), 7.79 - 7.82 (2 H, m), 10.27 (1 H, s), 12.22 (1 H, s).

Reference Example 211

To a mixture of water (5 ml) and zinc (379 mg) was added a solution of ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-nitropyridin-2-yl)oxy]phenyl}acrylate (455 mg) in acetic acid (5 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, the obtained residue was basified with a 8N aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give ethyl (2E)-3-[2-[(5-amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (307 mg, yield: 73%) as brown crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.2 Hz), 2.23 (3 H, s), 3.41 (3 H, s), 3.51 (2 H, s), 3.67 - 3.71 (2 H, m), 4.03 - 4.07 (2 H, m), 4.21 (2 H, q, J = 7.2 Hz), 6.38 (1 H, s), 6.41 (1 H, d, J = 15.9 Hz), 6.67 (1 H, dd, J = 8.7, 2.4 Hz), 6.96 (1 H, d, J = 2.4 Hz), 7.52 - 7.55 (2 H, m), 7.93 (1 H, d, J = 15.9 Hz).

Reference Example 212

To a solution of ethyl (2E)-3-[2-[(5-amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (300 mg) in tetrahydrofuran (10 ml) was added di-tert-butyl dicarbonate (880 mg), and the mixture was stirred at 60°C for 11 hr. The reaction mixture was concentrated, the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give ethyl (2E)-3-[2-({5-[(tert-butoxycarbonyl)amino]-3-methylpyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]acrylate (351 mg, yield: 92%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.29 (3 H, t, J = 7.2 Hz), 1.52 (9 H, s), 2.35 (3 H, s), 3.41 (3 H, s), 3.69 - 3.72 (2 H, m), 4.05 - 4.08 (2 H, m), 4.20 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 15.9 Hz), 6.34 - 6.40 (1 H, m), 6.49 (1 H, d, J = 2.7 Hz), 6.74 (1 H, dd, J = 8.7, 2.7 Hz), 7.57 (1 H, d, J = 8.7 Hz), 7.78 - 7.79 (1 H, m), 7.85 (1 H, d, J = 15.9 Hz), 7.93 (1H, s).

Reference Example 213

To a mixed solution of ethyl (2E)-3-[2-({5-[(tert-butoxycarbonyl)amino]-3-methylpyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]acrylate (351 mg) in tetrahydrofuran (3 ml) and ethanol (3 ml) was added a 1N aqueous sodium hydroxide solution (1.5 ml), and the mixture was stirred at 60°C for 1 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-3-[2-({5-[(tert-butoxycarbonyl)amino]-3-methylpyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (327 mg, yield: 99%) as colorless crystals. melting point 159.0-160.0°C.

Reference Example 214

To a mixture of ethylene glycol (34 ml) and pyridine (34 ml) was added dropwise chloro(triisopropyl)silane (10.7 ml) at room temperature over 20 min, and the mixture was stirred for 12 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The aqueous layer was washed with ethyl acetate, and the obtained organic layer was washed with water and saturated brine, dried, and concentrated. The obtained residue was subjected to column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:5, v/v) to give 2-[(triisopropylsilyl)oxy]ethanol (10.48 g, yield: 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.99 - 1.17 (21 H, m), 2.17 (1 H, t, J = 6.2 Hz), 3.58 - 3.71 (2 H, m), 3.74 - 3.85 (2 H, m).

Reference Example 215

To a mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (1.50 g), 2-[(triisopropylsilyl)oxy]ethanol (1.01 g), tributylphosphine (2.41 ml) and tetrahydrofuran (50 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.95 g) at room temperature, and the mixture was stirred for 16 hr. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:20 - 1:3, v/v) to give ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylate as a pale-yellow oil (2.02 g, yield: 89%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.97 - 1.15 (21 H, m), 1.28 (3 H, t, J = 7.1 Hz), 3.98 - 4.12 (4 H, m), 4.20 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 16.2 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 8.8, 2.5 Hz), 7.62 (1 H, d, J = 8.7 Hz), 7.68 (1 H, d, J = 16.2 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Example 216

A mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylate (1.22 g), a 1N aqueous sodium hydroxide solution (4.14 ml), tetrahydrofuran (3.2 ml) and ethanol (3.2 ml) was stirred at 50°C for 2 hr. The reaction mixture was concentrated, 1N hydrochloric acid (4.14 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was washed with diethyl ether-hexane, and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 2:1, v/v) to give (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylic acid (0.99 g, yield: 85%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.95 - 1.17 (21 H, m), 3.88 - 4.20 (4 H, m), 6.36 (1 H, d, J = 16.0 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.90 (1 H, dd, J = 8.7, 2.5 Hz), 7.64 (1 H, d, J = 8.9 Hz), 7.76 (1 H, d, J = 16.0 Hz), 8.02 (1 H, dd, J = 2.3, 0.4 Hz), 8.25 (1 H, dd, J = 2.3, 0.9 Hz).

Reference Example 217

To a mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (3.00 g), 1,3-diethoxypropan-2-ol (1.38 g), tributylphosphine (4.81 ml) and tetrahydrofuran (100 ml) was added 1,1'-(azodicarbonyl)dipiperidine (3.91 g) at room temperature, and the mixture was stirred for 16 hr. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:20 - 1:3, v/v) to give ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}acrylate as a colorless oil (1.97

g, yield: 49%). Crystallization from diethyl ether-hexane gave a white powder. melting point 66-67.5°C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.17 (6 H, t, J = 7.0 Hz), 1.28 (3 H, t, J = 7.2 Hz), 3.52 (4 H, qd, J = 7.0, 0.9 Hz), 3.59 - 3.74 (4 H, m), 4.20 (2 H, q, J = 7.0 Hz), 4.41 - 4.59 (1 H, m), 6.37 (1 H, d, J = 16.0 Hz), 6.79 (1 H, d, J = 2.5 Hz), 6.95 (1 H, dd, J = 8.8, 2.5 Hz), 7.61 (1 H, d, J = 8.7 Hz), 7.70 (1 H, d, J = 16.2 Hz), 8.01 (1 H, d, J = 2.3 Hz), 8.24 (1 H, dd, J = 2.2, 1.0 Hz).

Reference Example 218

A mixture of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}acrylate (1.96 g), a 1N aqueous sodium hydroxide solution (7.4 ml), tetrahydrofuran (3.5 ml) and ethanol (3.5 ml) was stirred at 50°C for 2 hr. The reaction mixture was concentrated, 1N hydrochloric acid (7.4 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was recrystallized from ethyl acetate-hexane. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:25 - 1:5 - 1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}acrylic acid (407 mg, yield: 23%) as colorless crystals. melting point 62-63°C.

Reference Example 219

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (3.00 g) in N,N-dimethylformamide (10 ml) were added potassium carbonate (2.14 g), sodium iodide (1.74 g) and 2-(2-bromoethyl)-1,3-dioxolane (1.36 ml) at room temperature, and the mixture was stirred at 80°C for 12 hr. After cooling, water was added to the reaction mixture, and the mixture was

extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:1, v/v). The obtained crude crystals were recrystallized from diethyl ether-hexane to give ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}acrylate (2.75 g, yield: 73%) as a white powder. melting point 102-103°C.

Reference Example 220

A mixture of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}acrylate (2.71 g), a 1N aqueous sodium hydroxide solution (11.1 ml), tetrahydrofuran (11 ml) and ethanol (11 ml) was stirred at 50°C for 2 hr. The reaction mixture was concentrated, 1N hydrochloric acid (11.1 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was recrystallized from ethyl acetate-hexane to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}acrylic acid (2.11 g, yield: 83%) as colorless crystals. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:10 - 2:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point 157-158.5°C.

Reference Example 221

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (4.02 g) in N,N-dimethylformamide (25 ml) were added potassium carbonate (2.87 g), sodium iodide (3.12 g) and 2-(bromomethyl)tetrahydrofuran (2.34 ml) at room temperature, and the mixture was stirred at 80°C for 16 hr. After cooling, water was added to the reaction mixture, and extracted with

ethyl acetate-hexane (1:1, v/v). The organic layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:3, v/v). The obtained crude crystals were recrystallized from diisopropyl ether-hexane to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylate (1.85 g, yield: 38%) as a white powder. melting point 84-86°C.

Reference Example 222

A mixture of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylate (1.75 g), a 1N aqueous sodium hydroxide solution (7.4 ml), tetrahydrofuran (3.5 ml) and ethanol (3.5 ml) was stirred at 50°C for 2 hr. 1N Hydrochloric acid (7.4 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from diethyl ether-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylic acid (0.79 g, yield: 48%) as white crystals. melting point 106-109°C.

Reference Example 223

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (4.02 g) in N,N-dimethylformamide (25 ml) were added potassium carbonate (2.87 g), sodium iodide (3.12 g) and 2-chloropyrimidine (2.38 g) at room temperature, and the mixture was stirred at 80°C for 12 hr. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to NH-silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 -

1:2, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(pyrimidin-2-yloxy)phenyl]acrylate (2.50 g, yield: 54%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.2 Hz), 4.22 (2 H, q, J = 7.2 Hz), 6.47 (1 H, d, J = 16.2 Hz), 7.04 - 7.13 (2 H, m), 7.20 (1 H, dd, J = 8.7, 2.5 Hz), 7.75 (1 H, d, J = 3.6 Hz), 7.79 (1 H, d, J = 11.1 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz), 8.59 (2 H, d, J = 4.9 Hz).

Reference Example 224

A mixture of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(pyrimidin-2-yloxy)phenyl]acrylate (2.38 g), a 1N aqueous sodium hydroxide solution (11 ml), tetrahydrofuran (12 ml) and ethanol (12 ml) was stirred at 50°C for 2 hr. The reaction mixture was concentrated, 1N hydrochloric acid (11 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:25 - 1:5 - 1:1, v/v) to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(pyrimidin-2-yloxy)phenyl]acrylic acid (1.26 g, yield: 54%) as a white amorphous powder.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:6.49 (1 H, d, J = 16.0 Hz), 7.03 - 7.14 (2 H, m), 7.22 (1 H, dd, J = 8.6, 2.4 Hz), 7.78 (1 H, d, J = 8.7 Hz), 7.86 (1 H, d, J = 16.2 Hz), 8.02 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz), 8.60 (2 H, d, J = 4.9 Hz).

Reference Example 225

To a mixture of methyl 3-isopropoxy-1H-pyrazole-5-carboxylate (1.55 g), potassium carbonate (1.75 g) and N,N-dimethylformamide (15 ml) was added 3-chloro-2-(chloromethyl)-5-(trifluoromethyl)pyridine (1.94 g) at 0°C, and the mixture was stirred at room temperature for 15 hr. Water was poured

into the reaction mixture, and the mixture was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:49 - 1:9, v/v) to give methyl 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazole-5-carboxylate (1.63 g, yield: 51%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.3 Hz), 3.80 (3 H, s), 4.63 - 4.76 (1 H, m), 5.92 (2 H, s), 6.30 (1 H, s), 7.87 - 7.92 (1 H, m), 8.59 - 8.63 (1 H, m).

Reference Example 226

A mixture of methyl 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazole-5-carboxylate (1.92 g), a 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and methanol (10 ml) was stirred at 50°C for 1 hr. The reaction mixture was concentrated, 1N hydrochloric acid (100 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazole-5-carboxylic acid (1.63 g, yield: 88%) as colorless crystals. melting point 124-125°C.

Reference Example 227

A mixture of N,O-dimethylhydroxylamine hydrochloride (515 mg), triethylamine (534 mg) and N,N-dimethylformamide (30 ml) was stirred at room temperature for 30 min, 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazole-5-carboxylic acid (1.60 g), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (1.01 g) and 1-hydroxybenzotriazole monohydrate (809 mg) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N

hydrochloric acid and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:4, v/v) to give 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide (1.37 g, yield: 77%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.33 (6 H, d, J = 6.0 Hz), 3.28 (3 H, s), 3.72 (3 H, s), 4.67 - 4.80 (1 H, m), 5.92 (2 H, s), 6.30 (1 H, s), 7.86 - 7.90 (1 H, m), 8.53 - 8.57 (1 H, m).

Reference Example 228

To a solution of 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide (1.36 g) in tetrahydrofuran (25 ml) was added a 1.5 M diisobutylaluminum hydride solution in toluene (3.4 ml) at 0°C, and the mixture was stirred for 2 hr. Furthermore, to the reaction mixture was added a 1.5 M diisobutylaluminum hydride solution in toluene (1.5 ml) at 0°C, and the mixture was stirred for 30 min. Methanol was added to quench the reaction. The reaction mixture was poured into a 10% aqueous Rochelle salt solution, and the mixture was stirred and extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:4, v/v) to give 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazole-5-carbaldehyde (640 mg, yield: 55%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.34 (6 H, d, J = 6.0 Hz), 4.68 - 4.81 (1 H, m), 5.87 (2 H, s), 6.35 (1 H, s), 7.88 - 7.92 (1 H, m), 8.56 - 8.61 (1 H, m), 9.74 (1 H, s).

Reference Example 229

Under ice-cooling, to a solution of ethyl diethylphosphonoacetate (619 mg) in N,N-dimethylformamide (6.0 ml) was added sodium hydride (60% in oil, 96 mg), and the mixture was stirred at room temperature for 30 min. The

reaction mixture was ice-cooled again, a solution of 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazole-5-carbaldehyde (640 mg) in tetrahydrofuran (6.0 ml) was added, and the mixture was stirred at 0°C for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give ethyl (2E)-3-(1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazol-5-yl)acrylate (640 mg, yield: 83%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.31 (3 H, t, J = 7.2 Hz), 1.31 (6 H, d, J = 6.0 Hz), 4.23 (2 H, d, J = 7.2 Hz), 4.61 - 4.74 (1 H, m), 5.56 (2 H, s), 6.02 (1 H, s), 6.32 (1 H, d, J = 15.6 Hz), 7.48 (1 H, d, J = 15.6 Hz), 7.91 - 7.95 (1 H, m), 8.65 - 8.70 (1 H, m).

Reference Example 230

A mixture of methyl (2E)-3-(1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazol-5-yl)acrylate (640 mg), a 1N aqueous sodium hydroxide solution (3.0 ml), tetrahydrofuran (6.0 ml) and ethanol (6.0 ml) was stirred at 50°C for 1 hr, 1N hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained crude crystals were recrystallized from hexane-ethyl acetate to give (2E)-3-(1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazol-5-yl)acrylic acid (460 mg, yield: 77%) as colorless crystals. melting point 130-132°C.

Reference Example 231

To a solution of benzyl alcohol (3.06 g) in dichloromethane (150 ml) was added chlorosulfonylisocyanate (2.55 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (8.0 ml) was added to the reaction mixture, and

the mixture was stirred for 1 hr. 4-Methylcyclohexylamine (18.0 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave benzyl {[(4-methylcyclohexyl)amino]sulfonyl}carbamate (6.64 g, yield: 72%) as white crystals. Recrystallization from ethyl acetate-diisopropyl ether gave white feather crystals. melting point 153-155°C.

Reference Example 232

To a solution of benzyl {[(4-methylcyclohexyl)amino]sulfonyl}carbamate (6.34 g) in tetrahydrofuran (40 ml) and ethanol (40 ml) was added 10% palladium-carbon (3.41 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated, and the filtrate was concentrated. Recrystallization of the obtained residue from ethyl acetate-hexane gave N-(4-methylcyclohexyl)sulfamide (3.19 g, yield: 86%) as white mica crystals. melting point 109-110°C.

Reference Example 233

To a solution of benzyl alcohol (3.02 g) in dichloromethane (150 ml) was added chlorosulfonylisocyanate (2.55 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (8.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-(2-Thienyl)ethylamine (5.0 g) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained

residue was washed with diisopropyl ether. Recrystallization from ethyl acetate-hexane gave benzyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate (8.29 g, yield: 87%) as white crystals. Recrystallization from ethyl acetate-diisopropyl ether gave white crystals. melting point 129-131°C.

Reference Example 234

A solution of benzyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate (6.34 g) in 25% w/w hydrobromic acid-acetic acid (25 ml) and acetic acid (10 ml) was stirred at room temperature for 1 hr, and then at 45°C for 30 min. The reaction mixture was poured into an ice-cooled saturated aqueous sodium hydrogencarbonate solution, and diluted with ethyl acetate. The organic layer was washed with water and saturated brine, filtrated, dried ($MgSO_4$), filtrated and concentrated, and the filtrate was concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 1:1, v/v) to give a pale brown solid. Recrystallization from ethyl acetate-hexane gave N-[2-(2-thienyl)ethyl]sulfamide (3.21 g, yield: 66%) as a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave white crystals.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.13 (2 H, t, J = 6.6 Hz), 3.43 (2 H, q, J = 6.5 Hz), 4.36 - 4.60 (3 H, m), 6.89 (1 H, dd, J = 3.5, 1.0 Hz), 6.96 (1 H, dd, J = 5.2, 3.5 Hz), 7.19 (1 H, dd, J = 5.2, 1.2 Hz).

Reference Example 235

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylate (3.00 g) in tetrahydrofuran (30 ml) was added 5% palladium-carbon (1.51 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl

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acetate-hexane (hexane alone to 2:3, v/v) to give a colorless oil.

To a solution of the obtained oil in tetrahydrofuran (5 ml) and ethanol (5 ml) was added a 1N aqueous sodium hydroxide solution (15 ml), and the mixture was stirred at 50°C for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid (15 ml) and a small amount of toluene were added to the reaction mixture, and the mixture was concentrated. The obtained residue was dissolved in ethyl acetate, and the solution was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylpropanoic acid (1.25 g, yield: 52%) as white crystals. melting point 129.5-131.0°C.

Reference Example 236

To a solution of 2-(benzyloxy)-4-(2-methoxyethoxy)benzaldehyde (11.92 g) in tetrahydrofuran (80 ml) were added methyl methoxyacetate (6.16 g) and potassium t-butoxide (6.81 g), and the mixture was stirred at room temperature for 5 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:2, v/v) to give a yellow oil.

To a solution of the obtained oil in methanol (100 ml) was added 10% palladium-carbon (5.01 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give methyl 3-[2-hydroxy-4-(2-

methoxyethoxy)phenyl]-2-methoxypropanoate (3.45 g, yield: 29%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.91 - 3.11 (2 H, m), 3.44 (3 H, s), 3.49 (3 H, s), 3.70 - 3.77 (5 H, m), 4.01 - 4.12 (3 H, m), 6.43 (1 H, dd, J = 8.3, 2.6 Hz), 6.51 (1 H, d, J = 2.6 Hz), 6.91 (1 H, d, J = 8.3 Hz), 7.69 (1 H, s).

Reference Example 237

To a solution of methyl 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoate (1.84 g) in N,N-dimethylformamide (30 ml) was added under ice-cooling sodium hydride (60% in oil, 311 mg), and the mixture was subsequently stirred for 30 min. Then, 2,3-dichloro-5-(trifluoromethyl)pyridine (1.0 ml) was added, and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give methyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoate (2.26 g, yield: 75%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.76 - 2.94 (2 H, m), 3.28 (3 H, s), 3.44 (3 H, s), 3.67 (3 H, s), 3.71 - 3.76 (2 H, m), 3.95 (1 H, dd, J = 7.9, 5.5 Hz), 4.07 - 4.12 (2 H, m), 6.69 - 6.72 (1 H, m), 6.82 (1 H, dd, J = 8.6, 2.5 Hz), 7.22 - 7.30 (1 H, m), 7.99 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.3, 0.9 Hz).

Reference Example 238

To a solution of methyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoate (2.26 g) in tetrahydrofuran (5 ml) and methanol (5 ml) was added a 1N aqueous sodium hydroxide solution (15 ml), and the mixture was stirred at 50°C for 30 min. After allowing to cool to room temperature, 1N

hydrochloric acid (15 ml) and a small amount of toluene were added to the reaction mixture, and the mixture was concentrated. The obtained residue was dissolved in ethyl acetate, and the mixture was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 alone to 65:35, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoic acid (1.19 g, yield: 54%) as white crystals. melting point 93-96°C.

Reference Example 239

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylate (2.37 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (15 ml), and the mixture was stirred at 50°C for 4 hr. A 1N aqueous sodium hydroxide solution (15 ml) was added to the reaction mixture, and the mixture was further stirred for 3 hr. After allowing to cool to room temperature, 1N hydrochloric acid (30 ml) was added to the reaction mixture, and the mixture was diluted with toluene and concentrated. The residue was dissolved in ethyl acetate, and the organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give a white solid. The obtained solid was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (35:65 - 7:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (741 mg, yield: 33%) as white needles. melting point 122.0-122.5°C.

Reference Example 240

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]methanol (9.92 g) in tetrahydrofuran (60 ml) and diethyl ether (240 ml) were added pyridine (0.50 ml) and thionyl chloride (4.5 ml) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution, and saturated brine; dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:9, v/v) to give 3-chloro-2-[2-(chloromethyl)-5-(2-methoxyethoxy)phenoxy]-5-(trifluoromethyl)pyridine (8.06 g, yield: 77%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 108-111°C.

Reference Example 241

To a solution of benzyl alcohol (3.06 g) in dichloromethane (150 ml) was added chlorosulfonyl isocyanate (2.55 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (8.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 1-Pentylamine (16.0 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave benzyl [(pentylamino)sulfonyl]carbamate (8.18 g, yield: 96%) as white crystals. melting point 142.5-143.0°C.

Reference Example 242

To a solution of benzyl [(pentylamino)sulfonyl]carbamate (5.83 g) in tetrahydrofuran (50 ml) and ethanol (50 ml) was added 10% palladium-carbon (3.11 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4

hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was recrystallized from ethyl acetate-diisopropyl ether to give N-pentylsulfamide (3.15 g, yield: 98%) as white mica crystals. melting point 60-63°C.

Reference Example 243

To a solution of ethyl diphenylphosphonoacetate (1.08 g) in tetrahydrofuran (50 ml) was added a Triton B (trade name) 40%-methanol solution (1.60 ml) at -78°C, 15 min later, a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzaldehyde (1.15 g) in tetrahydrofuran (15 ml) was added dropwise, and the mixture was stirred for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 35:65, v/v) to give ethyl (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylate (1.12 g, yield: 82%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.1 Hz), 3.43 (3 H, s), 3.72 - 3.77 (2 H, m), 4.08 - 4.19 (4 H, m), 5.83 (1 H, d, J = 12.4 Hz), 6.70 (1 H, d, J = 2.2 Hz), 6.83 (1 H, d, J = 12.4 Hz), 6.83 - 6.89 (1 H, m), 7.78 (1 H, d, J = 8.8 Hz), 7.96 (1 H, d, J = 1.9 Hz), 8.24 (1 H, dd, J = 2.1, 1.0 Hz).

Reference Example 244

To a solution of ethyl (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylate (1.12 g) in tetrahydrofuran (4 ml), ethanol (4 ml) and water (4 ml) was added lithium hydroxide monohydrate (256 mg) under ice-cooling, and the mixture was stirred for 1 hr. Under ice-cooling, lithium hydroxide monohydrate (412 mg) was further added, and the mixture was stirred for 30 min. 1N Hydrochloric acid (16 ml) was added to the reaction mixture, and the mixture was diluted

with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (780 g, yield: 74%) as white crystals. melting point 131.8-132.0°C.

Reference Example 245

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.00 g) in tetrahydrofuran (100 ml) were added tributylphosphine (5.40 ml), 2-{[tert-butyl(diphenyl)silyl]oxy}ethanol (5.82 g) and 1,1'-(azodicarbonyl)dipiperidine (4.97 g), and the mixture was stirred overnight at 50°C. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give ethyl (2E)-3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylate (7.51 g, yield: 87%) as a white oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.04 (9 H, s), 1.22 - 1.29 (3 H, m), 3.98 (2 H, t, J = 4.9 Hz), 4.06 - 4.15 (2 H, m), 4.15 - 4.27 (2 H, m), 6.36 (1 H, d, J = 16.0 Hz), 6.65 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.7, 2.4 Hz), 7.32 - 7.49 (6 H, m), 7.61 (1 H, d, J = 8.9 Hz), 7.65 - 7.78 (5 H, m), 8.01 (1 H, d, J = 2.3 Hz), 8.23 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Examples 246, 247

To a solution of ethyl (2E)-3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylate (7.02 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (25 ml) at room temperature, and the mixture was stirred for 4 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted

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with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give (2E)-3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylic acid (789 mg yield: 12%) (Reference Example 246) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.04 (9 H, s), 3.98 (2 H, t, J = 5.2 Hz), 4.10 (2 H, t, J = 4.7 Hz), 6.37 (1 H, d, J = 16.0 Hz), 6.64 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.7, 1.7 Hz), 7.30 - 7.47 (6 H, m), 7.62 (1 H, d, J = 8.7 Hz), 7.68 (4 H, dd, J = 7.8, 1.6 Hz), 7.75 (1 H, d, J = 16.0 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.06 - 8.30 (1 H, m).

Then, a white solid was obtained. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]acrylic acid monohydrate (132 mg, yield: 3%) (Reference Example 247) as white crystals. melting point 153.0-153.2°C.

Reference Example 248

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (2.60 g) in N,N-dimethylformamide (20 ml) were added potassium carbonate (2.20 g) and 4-fluoronitrobenzene (1.50 ml), and the mixture was stirred overnight at room temperature, and then at 50°C for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give ethyl (2E)-3-[4-(2-methoxyethoxy)-2-(4-nitrophenoxy)phenyl]acrylate (3.97 g, quant.) as a yellow

solid. Recrystallization from ethyl acetate-hexane gave pale-yellow crystals as 0.3 hydrate. melting point 61-64°C.

Reference Example 249

To a solution of ethyl (2E)-3-[4-(2-methoxyethoxy)-2-(4-nitrophenoxy)phenyl]acrylate (3.89 g) in ethanol (50 ml) and tetrahydrofuran (10 ml) was added 10% palladium-carbon (0.91 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hr. The reaction mixture was filtrated and the filtrate was concentrated to give ethyl (2E)-3-[2-(4-aminophenoxy)-4-(2-methoxyethoxy)phenyl]acrylate (2.97 g, yield: 84%) as a pale-brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.22 (3 H, t, J = 7.1 Hz), 2.56 - 2.72 (2 H, m), 2.94 (2 H, t, J = 7.7 Hz), 3.40 (3 H, s), 3.57 (2 H, s), 3.63 - 3.71 (2 H, m), 3.93 - 3.99 (2 H, m), 4.10 (2 H, q, J = 7.1 Hz), 6.31 (1 H, d, J = 2.5 Hz), 6.51 (1 H, dd, J = 8.5, 2.5 Hz), 6.61 - 6.71 (2 H, m), 6.74 - 6.88 (2 H, m), 7.09 (1 H, d, J = 8.2 Hz).

Reference Example 250

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)-2-methylacrylate (4.61 g) in N,N-dimethylformamide (20 ml) were added potassium carbonate (3.12 g) and isopropyl iodide (2.0 ml), and the mixture was stirred at 50°C for 1 hr. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylate (3.46 g, yield: 68%) as white crystals. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 61.0-62.0°C.

Reference Example 251

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylate (3.46 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (20 ml), and the mixture was stirred at 50°C for 2 hr. After allowing to cool to room temperature, 1N hydrochloric acid (20 ml) was added to the reaction mixture, and the mixture was concentrated and diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 7:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (2.02 g, yield: 62%) as white crystals. melting point 114.4-114.5°C.

Reference Example 252

To a solution of benzyl alcohol (3.05 g) in dichloromethane (60 ml) was added chlorosulfonyl isocyanate (2.50 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (8.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Phenylethylamine (8.0 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave benzyl {[(2-phenylethyl)amino]sulfonyl}carbamate (8.27 g, yield: 88%) as white crystals. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 120.0-121.0°C.

Reference Example 253

To a solution of benzyl {[(2-phenylethyl)amino]sulfonyl}carbamate (7.97 g) in ethanol (100 ml) was added 10% palladium-carbon (7.51 g), and the mixture

was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtrated, and the filtrate was concentrated. Recrystallization of the obtained residue from ethyl acetate-hexane gave N-(2-phenylethyl)sulfamide (4.45 g, yield: 93%) as white crystals. melting point 61.8-62.0°C.

Reference Example 254

To a solution of benzyl alcohol (3.05 g) in dichloromethane (60 ml) was added chlorosulfonyl isocyanate (2.50 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (8.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 3-Methoxypropylamine (8.0 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave benzyl {[(3-methoxypropyl)amino]sulfonyl}carbamate (1.14 g, yield: 13%) as white crystals. melting point 91-93°C.

Reference Example 255

To a solution of benzyl {[(3-methoxypropyl)amino]sulfonyl}carbamate (1.11 g) in ethanol (5 ml) was added 10% palladium-carbon (1.22 g), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtrated and the filtrate was concentrated to give N-(3-methoxypropyl)sulfamide (631 mg, quant.) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.86 (2 H, tt, J = 5.9, 5.9 Hz), 3.26 (2 H, t, J = 6.2 Hz), 3.34 (3 H, s), 3.52 (2 H, t, J = 5.7 Hz), 4.69 (2 H, br. s.).

Reference Example 256

To a solution of benzyl alcohol (3.05 g) in dichloromethane (60 ml) was added chlorosulfonyl isocyanate

(2.50 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (8.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Isopropoxyethylamine (8.0 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave benzyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (7.91 g, yield: 89%) as white crystals. melting point 88-89°C.

Reference Example 257

To a solution of benzyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (7.76 g) in ethanol (50 ml) was added 10% palladium-carbon (7.01 g), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtrated and the filtrate was concentrated to give N-(2-isopropoxyethyl)sulfamide (4.44 g, yield: 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.17 (6 H, d, J = 6.0 Hz), 3.24 - 3.37 (2 H, m), 3.49 - 3.72 (3 H, m), 4.30 - 5.00 (3 H, m).

Reference Example 258

To a solution of benzyl alcohol (5.41 g) in acetonitrile (500 ml) was added chlorosulfonyl isocyanate (4.40 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (12.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 1-(Tetrahydrofuran-2-yl)methanamine (10.5 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to

give a white solid. Recrystallization from ethyl acetate-hexane gave benzyl {[(tetrahydrofuran-2-ylmethyl)amino]sulfonyl}carbamate (14.7 g, yield: 94%) as white crystals. melting point 96-97°C.

Reference Example 259

To a solution of benzyl {[(tetrahydrofuran-2-ylmethyl)amino]sulfonyl}carbamate (14.2 g) in ethanol (200 ml) was added 10% palladium-carbon (5.21 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 hr. The reaction mixture was filtrated and the filtrate was concentrated to give N-(tetrahydrofuran-2-ylmethyl)sulfamide (8.35 g, quant.) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.52 - 1.70 (1 H, m), 1.85 - 2.08 (3 H, m), 3.07 - 3.20 (1 H, m), 3.24 - 3.34 (1 H, m), 3.72 - 3.83 (1 H, m), 3.88 (1 H, ddd, J = 8.3, 6.7 Hz), 4.05 - 4.13 (1 H, m), 4.77 (3 H, br. s.).

Reference Example 260

A solution of 3-(methylthio)propan-1-ol (5.30 g), triethylamine (10.5 ml) and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.86 g) in toluene (50 ml) was ice-cooled, and p-toluenesulfonyl chloride (14.3 g) in toluene (50 ml) was added dropwise to the solution under a nitrogen atmosphere. After completion of the dropwise addition, and the mixture was allowed to warm to room temperature and stirred for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give 3-(methylthio)propyl 4-methylbenzenesulfonate (12.2 g, yield: 94%) as a colorless oil. MS m/z 261 (MH^+).

Reference Example 261

To a solution of 3-(methylthio)propyl 4-methylbenzenesulfonate (12.2 g) in methanol (250 ml) was added

dropwise a solution of Oxone (trade name) (57.7 g) in water (250 ml) under ice-cooling. After completion of the dropwise addition, and the mixture was stirred for 20 hr while allowing to warm to room temperature. Methanol was evaporated under reduced pressure, and the mixture was diluted with water. The organic product was extracted with ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and concentrated under reduced pressure. The precipitated crystals were washed with ethyl acetate-heptane to give 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate (13.1 g, yield: 96%) as colorless crystals. MS m/z 293 (MH^+).

Reference Example 262

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.00 g) in N,N-dimethylformamide (50 ml) were added potassium carbonate (2.67 g) and 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate (4.46 g), and the mixture was stirred at 50°C for 3 hr. After allowing to cool to room temperature, 1N hydrochloric acid was added to the reaction mixture, the resulting solid was collected by filtration and washed with water to give ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]phenyl}acrylate (6.34 g, yield: 97%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 190.6-191.0°C.

Reference Example 263

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]phenyl}acrylate (6.14 g) in tetrahydrofuran (30 ml) and ethanol (30 ml) was added a 1N aqueous sodium hydroxide solution (30 ml), and the mixture was stirred at 50°C for 3 hr. After allowing to cool to room temperature, 1N hydrochloric acid (30 ml) was added to the reaction mixture, and the resulting solid was collected by filtration and washed with water to give a white solid. The

solid was recrystallized from aqueous ethanol to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]phenyl}acrylic acid (4.83 g, yield: 83%) as white crystals. melting point 202-203°C.

Reference Examples 264, 265

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (10.0 g) in tetrahydrofuran (300 ml) were added tributylphosphine (10.5 ml), 3-methylbutane-1,3-diol (4.0 ml) and 1,1'-(azodicarbonyl)dipiperidine (9.76 g), and the mixture was stirred overnight at 50°C. Then, tributylphosphine (10.5 ml), 3-methylbutane-1,3-diol (4.0 ml) and 1,1'-(azodicarbonyl)dipiperidine (9.76 g) were added, and the mixture was stirred at 50°C for 1 hr. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 45:55, v/v). The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-3-methylbutoxy)phenyl]acrylate (Reference Example 264) (1.46 g, yield: 12%) as a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave white crystals as 0.5 hydrate. melting point 63.5-66.0°C.

Then, ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-1,1-dimethylpropoxy)phenyl]acrylate (Reference Example 265) (0.71 g, yield: 6%) was obtained as an orange oil.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 1.20 (3 H, t, J = 7.2 Hz), 1.32 (6 H, s), 1.87 (2 H, t, J = 7.5 Hz), 3.55 - 3.62 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.40 (1 H, t, J = 5.4 Hz), 6.57 (1 H, d, J = 16.2 Hz), 6.96 (1 H, s), 6.94 - 6.99 (1 H, m), 7.55 (1 H, d, J = 16.2 Hz), 8.50 - 8.50 (1 H, m), 8.63 (1 H, d, J = 2.0

Hz).

Reference Example 266

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-3-methylbutoxy)phenyl]acrylate (1.20 g) in tetrahydrofuran (3 ml) and ethanol (3 ml) was added a 1N aqueous sodium hydroxide solution (6.0 ml), and the mixture was stirred at 50°C for 30 min. A 1N aqueous sodium hydroxide solution (1.0 ml) was added to the reaction mixture, and the mixture was further stirred for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid (7.0 ml) was added to the reaction mixture, and diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-3-methylbutoxy)phenyl]acrylic acid (957 mg, yield: 85%) as white crystals. melting point 192-194°C.

Reference Example 267

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-1,1-dimethylpropoxy)phenyl]acrylate (0.71 g) in acetonitrile (6 ml) were added diisopropylethylamine (384 μl) and chloromethyl methyl ether (170 μl) at room temperature. Then, diisopropylethylamine (384 μl) and chloromethyl methyl ether (170 μl) were added 4 times in total every one hour, and the mixture was further stirred at room temperature for 1 hr. Water was added to the reaction mixture and diluted with ethyl acetate. The organic layer was washed with water, 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methoxymethoxy)-1,1-

dimethylpropoxy]phenyl}acrylate (977 mg, quant.) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.8 Hz), 1.38 (6 H, s), 1.96 - 2.07 (2 H, m), 3.35 (3 H, s), 3.74 (2 H, t, J = 7.2 Hz), 4.20 (2 H, q, J = 7.1 Hz), 4.62 (2 H, s), 6.40 (1 H, d, J = 16.0 Hz), 6.78 (1 H, d, J = 2.3 Hz), 6.93 (1 H, dd, J = 8.7, 2.3 Hz), 7.60 (1 H, d, J = 8.7 Hz), 7.72 (1 H, d, J = 16.0 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.23 (1 H, d, J = 0.8 Hz).

Reference Example 268

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.06 g) in N,N-dimethylformamide (26 ml) were added potassium carbonate (2.71 g), sodium iodide (5.87 g) and isobutylene oxide (50 ml), and the mixture was stirred overnight at 80°C. After allowing to cool to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]acrylate (4.67 g, yield: 78%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 79-83°C.

Reference Example 269

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]acrylate (1.77 g) in tetrahydrofuran (6 ml) and ethanol (6 ml) was added a 1N aqueous sodium hydroxide solution (9 ml), and the mixture was stirred at 50°C for 1 hr. After allowing to cool to room temperature, 1N hydrochloric acid (9 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and

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concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]acrylic acid (1.23 g, yield: 74%) as white crystals. melting point 126.5-128.0°C.

Reference Example 270

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.10 g) in N,N-dimethylformamide (26 ml) were added potassium carbonate (2.75 g), sodium iodide (5.90 g) and 1-bromo-3-methoxypropane (2.61 g), and the mixture was stirred at 50°C for 1 hr. After allowing to cool to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylate (4.22 g, yield: 70%) as white crystals. melting point 86.4-86.5°C.

Reference Example 271

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylate (2.38 g) in tetrahydrofuran (6 ml) and ethanol (6 ml) was added a 1N aqueous sodium hydroxide solution (12 ml), and the mixture was stirred at 50°C for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid (12 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was recrystallized from ethyl acetate-hexane to give a white

solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylic acid (1.47 g, yield: 76%) as white crystals. melting point 131-133°C.

Reference Example 272

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (11.5 g) in pyridine (25 ml) was added acetic anhydride (25 ml), and the mixture was stirred at room temperature for 1 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl acetate (8.80 g, yield: 76%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 52.5-53.0°C.

Reference Example 273

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl acetate (1.80 g) in toluene (20 ml) were added dimethylketene methyl trimethylsilyl acetal (3.50 ml) and magnesium perchlorate (1.44 g), and the mixture was stirred at 50°C for 3 hr. Water was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give methyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoate (1.78 g, yield: 90%) as a colorless

oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 (6 H, s), 2.73 (2 H, s), 3.43 (3 H, s), 3.66 (3 H, s), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.08 (2 H, dd, J = 5.5, 4.0 Hz), 6.66 (1 H, d, J = 2.4 Hz), 6.80 (1 H, dd, J = 8.6, 2.5 Hz), 7.15 - 7.24 (1 H, m), 7.98 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.3, 0.9 Hz).

Reference Example 274

To a solution of methyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoate (1.75 g) in tetrahydrofuran (4 ml) was added concentrated sulfuric acid-acetic acid-water (1:6:6, v/v, 8 ml), and the mixture was stirred at 80°C for 24 hr. After allowing to cool to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoic acid (1.36 g, yield: 80%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.20 (6 H, s), 2.77 (2 H, s), 3.43 (3 H, s), 3.73 (2 H, dd, J = 5.0, 3.9 Hz), 4.04 - 4.12 (2 H, m), 6.67 (1 H, d, J = 1.9 Hz), 6.81 (1 H, dd, J = 8.6, 1.6 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, s), 8.25 (1 H, d, J = 0.9 Hz).

Reference Example 275

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.17 g) in N,N-dimethylformamide (30 ml) were added potassium carbonate (3.64 g), sodium iodide (3.99 g) and 3-(2-methoxyethoxy)propyl bromide (5.25 g), and the mixture was stirred overnight at 50°C. After allowing to cool to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water

and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}acrylate (5.34 g, yield: 80%) as white crystals. melting point 65-67°C.

Reference Example 276

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}acrylate (2.92 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (13 ml), and the mixture was stirred at 50°C for 20 min. After allowing to cool to room temperature, 1N hydrochloric acid (13 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}acrylic acid (2.56 g, yield: 93%) as white crystals. melting point 103.0-104.0°C.

Reference Example 277

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.12 g) in N,N-dimethylformamide (30 ml) were added potassium carbonate (3.66 g), sodium iodide (3.89 g) and 1-bromo-2-(2-methoxyethoxy)ethane (3.60 ml), and the mixture was stirred overnight at 50°C. Then, potassium carbonate (7.21 g) and 1-bromo-2-(2-methoxyethoxy)ethane (7.20 ml) were added, and the mixture was further stirred for 4 hr. After allowing to cool to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed

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with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}acrylate (5.57 g, yield: 86%) as white crystals. melting point 76.6-76.8°C.

Reference Example 278

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}acrylate (3.32 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (15 ml), and the mixture was stirred at 50°C for 20 min. After allowing to cool to room temperature, 1N hydrochloric acid (15 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}acrylic acid (2.01 g, yield: 64%) as white crystals. melting point 133.9-134.0°C.

Reference Example 279

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylic acid (1.33 g) in tetrahydrofuran (40 ml) was added a palladium-activated carbon ethylenediamine complex (0.20 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 hr. The reaction mixture was filtrated, a palladium-activated carbon ethylenediamine complex (0.41 g) was added to the filtrate, and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hr. Methanol (40 ml) was added to the reaction mixture, and the mixture was stirred under a hydrogen atmosphere at room

temperature for 1 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propanoic acid (571 mg, yield: 43%) as white crystals. melting point 99.1-99.2°C.

Reference Example 280

To a solution of 2,4-dihydroxybenzaldehyde (24.5 g) in acetonitrile (200 ml) were added potassium bicarbonate (35.5 g) and 3-bromo-1-propanol (49.3 g), and the mixture was stirred at 80°C for 3 days. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give 2-hydroxy-4-(3-hydroxypropoxy)benzaldehyde (14.2 g, yield: 41%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.01 - 2.12 (2 H, m), 3.87 (2 H, q, J = 5.7 Hz), 4.18 (2 H, t, J = 6.1 Hz), 6.44 (1 H, d, J = 2.4 Hz), 6.54 (1 H, dd, J = 8.7, 2.3 Hz), 7.43 (1 H, d, J = 8.7 Hz), 9.72 (1 H, s), 11.47 (1 H, s).

Reference Example 281

To a solution of 2-hydroxy-4-(3-hydroxypropoxy)benzaldehyde (6.90 g) in acetone (170 ml) was added potassium carbonate (5.83 g) and chloromethyl methyl ether (3.20 ml) under ice-cooling, and the mixture was stirred overnight while allowing to warm to room temperature. Then, potassium carbonate (5.83 g) and chloromethyl methyl ether (3.20 ml) were added, and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic

layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:2, v/v) to give 4-(3-hydroxypropoxy)-2-(methoxymethoxy)benzaldehyde (4.67 g, yield: 55%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.53 - 1.62 (1 H, m), 1.97 - 2.12 (2 H, m), 3.53 (3 H, s), 3.87 (2 H, q, J = 5.7 Hz), 4.19 (2 H, t, J = 6.0 Hz), 5.29 (2 H, s), 6.62 (1 H, dd, J = 8.4, 2.0 Hz), 6.72 (1 H, d, J = 2.3 Hz), 7.81 (1 H, d, J = 8.9 Hz), 10.33 (1 H, s).

Reference Example 282

To a solution of 4-(3-hydroxypropoxy)-2-(methoxymethoxy)benzaldehyde (2.02 g) in N,N-dimethylformamide (40 ml) was added sodium hydride (60% in oil, 404 mg) with stirring under ice-cooling, and bromomethylcyclopropane (1.70 ml) was added 30 min later, and the mixture was stirred overnight at room temperature. Then, sodium hydride (60% in oil, 404 mg) and bromomethylcyclopropane (1.70 ml) was added at room temperature, and the mixture was stirred at room temperature for 3 hr and at 50°C for 2 hr. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give 4-[3-(cyclopropylmethoxy)propoxy]-2-(methoxymethoxy)benzaldehyde (1.16 g, yield: 47%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.15 - 0.23 (2 H, m), 0.46 - 0.63 (2 H, m), 0.87 - 1.14 (1 H, m), 2.01 - 2.16 (2 H, m), 3.28 (2 H, d, J = 6.8 Hz), 3.53 (3 H, s), 3.62 (2 H, t, J = 6.2 Hz), 4.10 - 4.16 (2 H, m), 5.28 (2 H, s), 6.53 - 6.65 (1 H, m), 6.70 (1 H, d, J = 2.3 Hz), 7.81 (1 H, d, J = 8.7 Hz), 10.32 (1 H, s).

Reference Example 283

To a solution of triethyl phosphonoacetate (1.06 g) in tetrahydrofuran (5 ml) was added sodium hydride (60% in oil, 189 mg) under ice-cooling, a solution of 4-[3-(cyclopropylmethoxy)propoxy]-2-(methoxymethoxy)benzaldehyde (1.16 g) in N,N-dimethylformamide (5 ml) was added dropwise 30 min later, and the mixture was stirred for 20 min while allowing to warm to room temperature. Then, triethyl phosphonoacetate (1.06 g) and sodium hydride (60% in oil, 189 mg) were added at room temperature, and the mixture was further stirred for 20 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a yellow oil.

To a solution of the obtained oil in acetone (8 ml) was added 1N hydrochloric acid (4 ml), and the mixture was stirred with heating under reflux for 12 hr. Then, 1N hydrochloric acid (4 ml) was added, and the mixture was further stirred for 3 hr. After allowing to cool to room temperature, a 1N aqueous sodium hydroxide solution (8 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a yellow oil.

To a solution of the obtained oil in N,N-dimethylformamide (15 ml) were added potassium carbonate (1.10 g) and 2,3-dichloro-5-(trifluoromethyl)pyridine (1.10 ml) at room temperature, and the mixture was stirred overnight at 50°C. After allowing to cool to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give ethyl (2E)-3-{2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(cyclopropylmethoxy)propoxy]phenyl}acrylate (0.66 g, yield: 34%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.14 - 0.23 (2 H, m), 0.45 - 0.57 (2 H, m), 0.88 - 1.11 (1 H, m), 1.28 (3 H, t, J = 7.1 Hz), 2.06 (2 H, tt, J = 6.2, 6.2 Hz), 3.26 (2 H, d, J = 6.8 Hz), 3.60 (2 H, t, J = 6.1 Hz), 4.09 (2 H, t, J = 6.0 Hz), 4.20 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 16.0 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.87 (1 H, dd, J = 8.6, 2.4 Hz), 7.63 (1 H, d, J = 8.9 Hz), 7.69 (1 H, d, J = 16.0 Hz), 8.01 (1 H, d, J = 1.7 Hz), 8.25 (1 H, dd, J = 2.3, 0.9 Hz).

Reference Example 284

To a solution of methyl 2,4-dihydroxy-3-methylbenzoate (14.8 g) in acetone (200 ml) were added potassium carbonate (22.4 g) and chloromethyl methyl ether (9.0 ml), and the mixture was stirred under ice-cooling for 2 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave methyl 2-hydroxy-4-(methoxymethoxy)-3-methylbenzoate (11.9 g, yield: 65%) as white crystals. melting point 73.8-74.0°C.

Reference Example 285

To a solution of methyl 2-hydroxy-4-(methoxymethoxy)-3-methylbenzoate (1.97 g) in N,N-dimethylformamide (16 ml) were added potassium carbonate (2.41 g) and 2,4-dichlorobenzyl chloride (1.50 ml), and the mixture was stirred overnight at 50°C. Water was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from hexane gave methyl 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoate (3.01 g, yield: 90%) as white crystals. melting point 98.8-99.0°C. A crude product was

obtained from the mother liquor (0.73 g).

Reference Example 286

To a solution of methyl 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoate (2.91 g) in tetrahydrofuran (8 ml) and methanol (8 ml) was added a 1N aqueous sodium hydroxide solution (16 ml), and the mixture was stirred overnight at 50°C. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoic acid (2.67 g, yield: 95%) as white crystals. melting point 173.5-174.0°C.

To a solution of a crude product of methyl 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoate (Reference Example 285, 0.73 g) in tetrahydrofuran (2 ml) and methanol (2 ml) was added a 1N aqueous sodium hydroxide solution (4 ml), and the mixture was stirred overnight at 50°C. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave a crude product (221 mg, yield: 31%) of 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoic acid as white crystals.

Reference Example 287

To a solution of 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoic acid (2.59 g) in N,N-dimethylformamide (60 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.01 g), triethylamine (2.90 ml), N,O-dimethylhydroxylamine hydrochloride (1.11 g), and 1-hydroxybenzotriazole hydrate (612 mg), and the mixture was stirred overnight at room temperature.

1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a crude product as a yellow oil.

To a solution of a crude product of 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzoic acid (Reference Example 57, 221 mg) in N,N-dimethylformamide (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (170 mg), triethylamine (0.25 ml), N,O-dimethylhydroxylamine hydrochloride (112 mg), and 1-hydroxybenzotriazole hydrate (137 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a crude product as a yellow oil.

The obtained crude products were combined, subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 1:1, v/v) to give 2-[(2,4-dichlorobenzyl)oxy]-N-methoxy-4-(methoxymethoxy)-N,3-dimethylbenzamide (3.04 g, yield: 97%) as a colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.18 (3 H, s), 3.23 (3 H, s), 3.50 (3 H, s), 3.57 (3 H, br. s.), 5.00 (2 H, s), 5.23 (2 H, s), 6.92 (1 H, d, J = 8.5 Hz), 7.15 (1 H, d, J = 8.5 Hz), 7.25 - 7.31 (1 H, m), 7.40 (1 H, d, J = 2.1 Hz), 7.58 (1 H, d, J = 8.3 Hz).

Reference Example 288

To a solution of 2-[(2,4-dichlorobenzyl)oxy]-N-methoxy-4-(methoxymethoxy)-N,3-dimethylbenzamide (3.04 g) in tetrahydrofuran (35 ml) was added a 1.5 M diisobutylaluminum hydride solution in toluene (7.5 ml) under ice-cooling, and the mixture was stirred for 1 hr. Then, under ice-cooling, a 1.5 M

diisobutylaluminum hydride solution in toluene (7.5 ml) was added, and the mixture was stirred overnight while allowing to warm to room temperature. Under ice-cooling, a saturated aqueous ammonium chloride solution (4.3 ml) was added dropwise to the reaction mixture, and the mixture was stirred for 1 hr. The mixture was filtered through celite, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzaldehyde (1.61 g, yield: 62%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 128.4-128.5°C.

Reference Example 289

To a solution of triethyl phosphonoacetate (1.06 g) in tetrahydrofuran (5 ml) was added sodium hydride (60% in oil, 189 mg) under ice-cooling, and 30 min later, a solution of 2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylbenzaldehyde (1.40 g) in N,N-dimethylformamide (5 ml) was added dropwise, and the mixture was stirred for 10 min while allowing to warm to room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give ethyl (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylphenyl]acrylate (1.79 g, quant.) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 110-112°C.

Reference Example 290

To a solution of ethyl (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(methoxymethoxy)-3-methylphenyl]acrylate (1.79 g) in acetone (16 ml) was added 1N hydrochloric acid (8 ml), and the mixture was stirred overnight with heating under reflux. After allowing to cool to room temperature, a 1N aqueous sodium hydroxide solution (8 ml) was added to the reaction mixture. The resulting solid was collected by

filtration and washed with cold water to give ethyl (2E)-3-{2-[(2,4-dichlorobenzyl)oxy]-4-hydroxy-3-methylphenyl}acrylate (0.43 g, yield: 29%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.31 (3 H, t, J = 7.2 Hz), 2.19 (3 H, s), 4.23 (2 H, q, J = 7.2 Hz), 4.88 (2 H, s), 5.16 (1 H, br. s.), 6.31 (1 H, d, J = 16.0 Hz), 6.66 (1 H, d, J = 8.5 Hz), 7.32 (1 H, dd, J = 8.3, 2.1 Hz), 7.36 (1 H, d, J = 8.7 Hz), 7.44 (1 H, d, J = 2.1 Hz), 7.59 (1 H, d, J = 8.3 Hz), 7.91 (1 H, d, J = 16.2 Hz).

Reference Example 291

To a solution of ethyl (2E)-3-{2-[(2,4-dichlorobenzyl)oxy]-4-hydroxy-3-methylphenyl}acrylate (0.43 g) in N,N-dimethylformamide (10 ml) were added potassium carbonate (0.47 g), sodium iodide (0.51 g) and 2-bromoethyl methyl ether (0.47 g), and the mixture was stirred overnight at 50°C and at 80°C for 2 hr. Then, potassium carbonate (0.47 g), sodium iodide (0.51 g) and 2-bromoethyl methyl ether (0.47 g) were added, and the mixture was further stirred for 2 hr. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:7, v/v) to give ethyl (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)-3-methylphenyl]acrylate (180 mg, yield: 36%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 92.0-92.5°C.

Reference Example 292

To a solution of ethyl (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)-3-methylphenyl]acrylate (170 mg) in tetrahydrofuran (2 ml) and ethanol (2 ml) was added a 1N aqueous sodium hydroxide solution (6.0 ml), and the mixture was stirred overnight at 80°C. After allowing to cool to room temperature, 1N hydrochloric acid (6.0 ml) was added to

the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)-3-methylphenyl]acrylic acid (99 mg, yield: 24%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.10 (3 H, s), 3.30 (3 H, s), 3.58 - 3.75 (2 H, m), 4.12 - 4.21 (2 H, m), 4.84 (2 H, s), 6.36 (1 H, d, J = 16.0 Hz), 6.88 (1 H, d, J = 8.7 Hz), 7.46 - 7.53 (1 H, m), 7.62 (2 H, d, J = 8.3 Hz), 7.69 (1 H, d, J = 2.1 Hz), 7.74 (1 H, d, J = 16.0 Hz).

Reference Example 293

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl}acrylate (2.53 g) in tetrahydrofuran (100 ml) were added tributylphosphine (3.30 ml), 2-(cyclopropyloxy)ethanol (0.80 g) and 1,1'-(azodicarbonyl)dipiperidine (2.47 g), and the mixture was stirred at 50°C for 30 min. The reaction mixture was concentrated, the obtained solid was washed with diisopropyl ether, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 35:65, v/v) to give ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}acrylate (2.21 g, yield: 72%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 75.4-75.9°C.

Reference Example 294

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}acrylate (2.01 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (10 ml), and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid (10

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ml) was added to the reaction mixture, and diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}acrylic acid (1.83 g, yield: 97%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 147-150°C.

Reference Example 295

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (5.12 g) in tetrahydrofuran (40 ml) was added a palladium-activated carbon ethylenediamine complex (0.23 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 hr. The reaction mixture was filtrated, a palladium-activated carbon ethylenediamine complex (0.50 g) was added to the filtrate, and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. Then, methanol (40 ml) was added, and the mixture was further stirred under a hydrogen atmosphere at room temperature for 15 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give an orange oil.

To a solution of the obtained oil in N,N-dimethylformamide (30 ml) were added potassium carbonate (1.79 g), sodium iodide (1.95 g) and 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (1.78 ml), and the mixture was stirred overnight at 60°C. After allowing to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give ethyl 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-

2-yl)ethoxy]phenyl}propanoate (0.77 g, yield: 19%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 (3 H, t, J = 7.1 Hz), 1.38 (3 H, s), 2.15 (2 H, t, J = 7.0 Hz), 2.56 (2 H, t, J = 7.5 Hz), 2.76 (2 H, t, J = 7.7 Hz), 3.85 - 4.00 (4 H, m), 4.01 - 4.15 (4 H, m), 6.65 (1 H, d, J = 2.6 Hz), 6.79 (1 H, dd, J = 8.5, 2.4 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Example 296

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (875 mg) in N,N-dimethylformamide (8 ml) were added potassium carbonate (695 mg) and 3-chloro-4-nitrobenzotrifluoride (894 mg), and the mixture was stirred at 50°C for 3 hr. After allowing to cool to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give a brown solid. Recrystallization from ethyl acetate-hexane gave ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[2-nitro-5-(trifluoromethyl)phenoxy]phenyl}acrylate (0.97 g, yield: 65%) as red-brown crystals. melting point 108-110°C.

Reference Example 297

To a solution of ethyl 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]propanoate (8.98 g) in N,N-dimethylformamide (60 ml) were added potassium carbonate (9.25 g) and benzyl bromide (5.0 ml), and the mixture was stirred at room temperature for 3 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with

ethyl acetate-hexane (hexane alone to 35:65, v/v) to give a colorless oil. The oil was dissolved in ethyl acetate, and the solution was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give ethyl 3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]propanoate (11.5 g, yield: 96%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 38-39°C.

Reference Example 298

To a solution of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]acrylate (2.44 g) in tetrahydrofuran (50 ml) was added 10% palladium-activated carbon (1.06 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give a yellow oil.

To a solution of the obtained oil in tetrahydrofuran (30 ml) was added a 1.5 M diisobutylaluminum hydride solution in toluene (12 ml) under ice-cooling, and the mixture was stirred for 20 min. Under ice-cooling, a saturated aqueous ammonium chloride solution was added dropwise to the reaction mixture, and the mixture was stirred for 1 hr. The mixture was filtered through celite, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]propan-1-ol (1.10 g, yield: 45%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 81.2-82.0°C.

Reference Example 299

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate in dichloromethane (100 ml) were

added pyridine (25.0 ml) and triflic anhydride (6.0 ml) under ice-cooling, and the mixture was stirred for 5 min. Water was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 35:65, v/v) to give ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[(trifluoromethyl)sulfonyl]oxy}phenyl)acrylate (12.56 g, quant.) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 37.1-37.3°C.

Reference Example 300

A mixture of ethyl (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (2.96 g), a palladium-activated carbon ethylenediamine complex (0.30 g) and methanol (200 ml) was stirred under a hydrogen atmosphere at room temperature for 3 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give ethyl 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propanoate (2.04 g, yield: 69%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 2.56 (2 H, t, J = 7.6 Hz), 2.78 (2 H, t, J = 7.8 Hz), 3.45 (3 H, s), 3.65 - 3.79 (2 H, m), 4.03 - 4.15 (4 H, m), 6.64 (1 H, d, J = 2.7 Hz), 6.77 (1 H, dd, J = 8.7, 2.7 Hz), 7.20 (1 H, d, J = 8.3 Hz), 7.77 (1 H, d, J = 2.7 Hz), 7.95 (1 H, d, J = 2.3 Hz).

Reference Example 301

Ethyl 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propanoate (2.04 g) was dissolved in diethyl ether (9.8 ml), a 1.5 M diisobutylaluminum hydride solution in toluene (8.2 ml) was added at 0°C, and the mixture was stirred at room temperature for 2.5 hr. Methanol and water

were added to the reaction mixture, the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 3:2, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propan-1-ol (1.48 g, yield: 81%) as colorless crystals. melting point 83.9-84.5°C.

Reference Example 302

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}acrylate (1.00 g) in tetrahydrofuran (10 ml) was added a 1.5 M diisobutylaluminum hydride solution in toluene (4.97 ml) under ice-cooling over 15 min, and the mixture was stirred for 1 hr. The reaction mixture was stirred at room temperature for 2 hr, sodium sulfate decahydrate (2.40 g) was added under ice-cooling, and the mixture was stirred for 12 hr. The insoluble material was filtered off and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:3, v/v) to give a white solid. Recrystallization from diethyl ether-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}prop-2-en-1-ol (40 mg, yield: 4%) as a white powder. melting point 52.5-54.5°C.

Reference Example 303

A mixture of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}prop-2-en-1-ol (135 mg), 5% palladium-carbon (16 mg) and ethyl acetate (5 ml) was stirred under a hydrogen atmosphere at room temperature for 2.5 hr. Palladium was filtered off, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:3, v/v) to give 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-

ethoxy-1-(ethoxymethyl)ethoxy]phenyl}propan-1-ol (120 mg, yield: 88%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.17 (6 H, t, J = 7.0 Hz), 1.75 - 1.91 (2 H, m), 2.46 - 2.63 (2 H, m), 3.45 - 3.57 (4 H, m), 3.57 - 3.71 (6 H, m), 4.38 - 4.51 (1 H, m), 6.74 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 8.5, 2.5 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, dd, J = 2.2, 0.5 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Example 304

A suspension of ethyl (2E)-3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylate (2.52 g) and 10% palladium-carbon in ethanol was stirred under a hydrogen atmosphere at room temperature for 4 hr. The reaction mixture was filtrated, and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 2:8, v/v) to give ethyl 3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate (1.88 g, yield: 74%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.04 (9 H, s), 1.14 - 1.32 (4 H, m), 2.57 (2 H, t, J = 7.8 Hz), 2.76 (2 H, t, J = 7.8 Hz), 3.89 - 4.19 (6 H, m), 6.63 (1 H, d, J = 2.7 Hz), 6.76 (1 H, dd, J = 8.5, 2.5 Hz), 7.21 (1 H, d, J = 8.7 Hz), 7.31 - 7.47 (6 H, m), 7.63 - 7.77 (4 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.25 (1 H, s).

Reference Example 305

Under ice-cooling, to a solution of ethyl 3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate (1.88 g) in diethyl ether (10 ml) was added dropwise a 1.5 M diisobutylaluminum hydride solution in toluene (5.6 ml), and the mixture was stirred while warming to room temperature over 4 hr. Saturated brine was added to the reaction mixture, the mixture was filtrated, and the filtrate was extracted with

ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 6:4, v/v) to give 3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propan-1-ol (1.06 g, yield: 60%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.04 (9 H, s), 1.36 (1 H, t, J = 5.7 Hz), 1.75 - 1.89 (2 H, m), 2.53 (2 H, t, J = 7.5 Hz), 3.61 (2 H, q, J = 6.1 Hz), 3.93 - 4.08 (4 H, m), 6.62 (1 H, d, J = 2.6 Hz), 6.78 (1 H, dd, J = 8.5, 2.6 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.31 - 7.46 (6 H, m), 7.64 - 7.75 (4 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.25 (1 H, d, J = 1.1 Hz).

Reference Example 306

Under ice-cooling, to a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propanoic acid (6.00 g) and triethylamine (2.26 g) in tetrahydrofuran (100 ml) was added isobutylchloroformate (2.24 g), and the mixture was stirred for 10 min. At the same temperature, methanol (50 ml), water (50 ml) and sodium borohydride (1.41 g) were added, and the mixture was stirred while warming to room temperature over 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v) to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propan-1-ol (3.86 g, yield: 66%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.2 Hz), 1.75 - 1.90 (2 H, m), 2.54 (2 H, t, J = 7.5 Hz), 3.61 (2 H, t, J = 6.3 Hz), 4.40 - 4.56 (1 H, m), 6.61 (1 H, d, J = 2.4 Hz), 6.78 (1 H, dd, J = 8.5, 2.4 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 1.7 Hz), 8.23 - 8.30 (1 H, m).

Reference Example 307

Under ice-cooling, to a mixed solution of 2-(benzyloxy)-4-(2-methoxyethoxy)benzaldehyde (5.00 g) and ethyl chloroacetate (1.85 ml) in tetrahydrofuran (60 ml)/tert-butanol (20 ml) was added potassium tert-butoxide (2.14 g), and the mixture was stirred at the same temperature for 1 hr. A 1N aqueous sodium hydroxide solution (20 ml) was added, and the mixture was stirred while warming to room temperature over 2 hr. Acetic acid (10 ml) was added, and the mixture was stirred at 50°C for 4 hr. The reaction solution was allowed to cool to room temperature, a 1N aqueous sodium hydroxide solution and ethyl acetate were added, and the mixture was washed successively with water and a saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v) to give [2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]acetaldehyde (1.80 g, yield: 34%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.45 (3 H, s), 3.62 (2 H, d, J = 2.1 Hz), 3.70 - 3.78 (2 H, m), 4.07 - 4.15 (2 H, m), 5.05 (2 H, s), 6.50 (1 H, dd, J = 8.3, 2.4 Hz), 6.62 (1 H, d, J = 2.3 Hz), 7.05 (1 H, d, J = 8.3 Hz), 7.28 - 7.43 (5 H, m), 9.68 (1 H, t, J = 2.1 Hz).

Reference Example 308

Under ice-cooling, to a mixture of [2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]acetaldehyde (1.80 g), methanol (25 ml) and water (25 ml) was added sodium borohydride (0.34 g) by small portions, and the mixture was stirred at the same temperature for 2 hr. 1N Hydrochloric acid was added to the reaction mixture, methanol was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 7:3, v/v) to give 2-[2-(benzyloxy)-4-(2-

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methoxyethoxy)phenyl]ethanol (1.50 g, yield: 83%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.88 (2 H, t, J = 6.4 Hz), 3.45 (3 H, s), 3.70 - 3.76 (2 H, m), 3.81 (2 H, t, J = 6.3 Hz), 4.06 - 4.13 (2 H, m), 5.04 (2 H, s), 6.47 (1 H, dd, J = 8.3, 2.4 Hz), 6.60 (1 H, d, J = 2.4 Hz), 7.08 (1 H, d, J = 8.3 Hz), 7.28 - 7.48 (5 H, m).

Reference Example 309

Under ice-cooling, to a mixed solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)benzaldehyde (10.0 g) and ethyl bromoacetate (11.6 g) in tetrahydrofuran (100 ml)/tert-butanol (100 ml) was added potassium tert-butoxide (7.78 g), and the mixture was stirred at the same temperature for 12 hr. The solvent was evaporated under reduced pressure, 8N aqueous sodium hydroxide solution (17 ml), water (34 ml) and tetrahydrofuran (50 ml) were added to the residue, and the mixture was stirred at room temperature for 2 hr. Acetic acid (200 ml) was added, and the mixture was stirred at 60°C for 4 hr. The reaction solution was allowed to cool to room temperature, and neutralized with a 8N aqueous sodium hydroxide solution and ethyl acetate was added. The mixture was washed successively with water and a saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 4:6, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]acetaldehyde (2.07 g, yield: 20%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.48 (3 H, s), 3.54 (2 H, d, J = 1.9 Hz), 5.18 (2 H, s), 6.91 (1 H, d, J = 2.7 Hz), 7.00 (1 H, dd, J = 8.5, 2.5 Hz), 7.22 - 7.28 (1 H, m), 7.99 (1 H, d, J = 1.9 Hz), 8.25 (1 H, s), 9.67 (1 H, t, J = 2.1 Hz).

Reference Example 310

Under ice-cooling, to a mixture of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]acetaldehyde (1.54 g), methanol (60 ml) and water (25 ml) was added sodium borohydride (0.23 g) by small portions, and the mixture was stirred at the same temperature for 2 hr. 1N Hydrochloric acid was added to the reaction mixture, methanol was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v) to give 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]ethanol (1.32 g, yield: 85%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.49 - 1.58 (1 H, m), 2.75 (2 H, d), 3.47 (3 H, d), 3.80 (2 H, d), 5.15 (2 H, d), 6.81 (1 H, d, J = 2.4 Hz), 6.96 (1 H, dd, J = 8.5, 2.4 Hz), 7.22 - 7.32 (1 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Example 311

To 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]ethyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.19 g) was added a 10% hydrochloric acid-methanol solution (5 ml), and the mixture was stirred at 40°C for 3 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 2-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)ethyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.085 g, yield: 48%)

as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.15 (6 H, d, J = 6.0 Hz), 2.87 (2 H, t, J = 6.7 Hz), 3.13 (2 H, q, J = 5.7 Hz), 3.44 - 3.65 (3 H, m), 4.36 (2 H, t, J = 6.6 Hz), 5.21 (1 H, s), 5.28 - 5.41 (1 H, m), 6.59 (1 H, d, J = 2.6 Hz), 6.73 (1 H, dd, J = 8.4, 2.5 Hz), 7.19 (1 H, d, J = 8.5 Hz), 7.61 (1 H, s), 8.03 (1 H, d, J = 2.1 Hz), 8.32 (1 H, d, J = 1.1 Hz).

Reference Example 312

A suspension of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]acrylate (9.5 g) and 10% palladium-carbon in ethanol (300 ml) was stirred under a hydrogen atmosphere at room temperature for 4 hr. The reaction mixture was filtrated, and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 2:8, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propanoate (8.1 g, yield: 85%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 - 1.30 (3 H, t, J = 7.2 Hz), 2.52 - 2.62 (2 H, m), 2.77 (2 H, t, J = 7.6 Hz), 3.47 (3 H, s), 4.09 (2 H, q, J = 7.2 Hz), 5.15 (2 H, s), 6.81 (1 H, d, J = 2.3 Hz), 6.88 - 6.99 (1 H, m), 7.24 (1 H, d, J = 8.3 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, s).

Reference Example 313

Under ice-cooling, to a solution of ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propanoate (8.0 g) in diethyl ether (30 ml) was added dropwise a 1.5 M diisobutylaluminum hydride solution in toluene (36.8 ml), and the mixture was stirred while warming to room temperature over 4 hr. Saturated brine was added to the reaction mixture, the mixture was filtrated, and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$),

and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propan-1-ol (5.18 g, yield: 72%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.36 (1 H, t, J = 5.6 Hz), 1.75 - 1.91 (2 H, m), 2.48 - 2.60 (2 H, m), 3.48 (3 H, s), 3.61 (2 H, q, J = 6.2 Hz), 5.15 (2 H, s), 6.80 (1 H, d, J = 2.4 Hz), 6.94 (1 H, dd, J = 8.5, 2.4 Hz), 7.24 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Reference Example 314

To 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (5.2 g) was added a 10% hydrochloric acid-methanol solution (50 ml), and the mixture was stirred at 40°C for 3 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 6:4, v/v) to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (3.9 g, yield: 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 (6 H, d, J = 6.1 Hz), 1.86 - 2.02 (2 H, m), 2.62 (2 H, t, J = 7.4 Hz), 3.24 (2 H, q, J = 5.6 Hz), 3.50 - 3.70 (3 H, m), 4.13 (2 H, t, J = 6.1 Hz), 5.34 (1 H, t, J = 5.9 Hz), 5.48 (1 H, br.s.), 6.64 (1 H, d, J = 2.3 Hz), 6.71 (1 H, dd, J = 8.1, 2.5 Hz), 7.14 (1 H, d, J = 8.3 Hz), 7.92 (1 H, br.s.), 8.03 (1 H, d, J = 2.3 Hz), 8.31 (1 H, s).

Reference Example 315

A mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate

(3.00 g), 4-bromobutyronitrile (1.72 g), potassium carbonate (2.14 g), sodium iodide (1.74 g) and N,N-dimethylformamide (20 ml) was stirred at 50°C for 15 hr. After cooling, the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]acrylate (3.30 g, yield: 94%) as colorless crystals. melting point 106-107°C.

Reference Example 316

A mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (3.00 g), 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (2.27 g), potassium carbonate (2.14 g), sodium iodide (1.74 g), and N,N-dimethylformamide (20 ml) was stirred at 50°C for 15 hr and at 80°C for 6 hr. After cooling, the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:1, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}acrylate (2.86 g, yield: 74%) as colorless crystals. melting point 90-91°C.

Reference Example 317

A mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (3.00 g), bromoacetone (1.59 g), potassium carbonate (2.14 g), sodium iodide (1.74 g) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained

solid was recrystallized from ethyl acetate-hexane to give ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-oxopropoxy)phenyl]acrylate (2.77 g, yield: 81%) as colorless crystals. melting point 167-168°C.

Reference Example 318

A mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (3.00 g), glycidyl isopropyl ether (4.50 g), potassium carbonate (6.42 g), sodium iodide (5.80 g), and N,N-dimethylformamide (20 ml) was stirred at 50°C for 15 hr and at 80°C for 6 hr. After cooling, the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:1, v/v) to give ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-3-isopropoxypropoxy)phenyl]acrylate (3.16 g, yield: 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.17 (6 H, d, J = 6.3 Hz), 1.28 (3 H, t, J = 7.2 Hz), 2.54 (1 H, d, J = 4.5 Hz), 3.48 - 3.68 (3 H, m), 4.00 - 4.24 (5 H, m), 6.37 (1 H, d, J = 16.2 Hz), 6.72 (1 H, s), 6.78 - 6.93 (1 H, m), 7.61 - 7.72 (2 H, m), 8.02 (1 H, s), 8.25 (1 H, s).

Reference Example 319

To a mixture of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]acrylate (3.25 g), tetrahydrofuran (15 ml), and ethanol (10 ml) was added a 1M sodium hydroxide solution (14.3 ml), and the mixture was stirred at 50°C for 2 hr. The reaction mixture was poured into water, and the mixture was neutralized with a 1M hydrochloric acid solution (14.4 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl

acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]acrylic acid (2.38 g, yield: 78%) as colorless crystals. melting point 183-185°C.

Reference Example 320

To a mixture of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-oxopropoxy)phenyl]acrylate (2.46 g), tetrahydrofuran (40 ml), and ethanol (10 ml) was added a 1M sodium hydroxide solution (11.1 ml), and the mixture was stirred at 50°C for 3 hr. The reaction mixture was poured into water, and the mixture was neutralized with a 1M hydrochloric acid solution (11.2 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-oxopropoxy)phenyl]acrylic acid (311 mg, yield: 14%) as colorless crystals. melting point 179-180°C.

Reference Example 321

To a mixture of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}acrylate (2.75 g), tetrahydrofuran (10 ml), and ethanol (10 ml) was added a 1M sodium hydroxide solution (11.0 ml), and the mixture was stirred at 50°C for 3 hr. The reaction mixture was poured into water, and the mixture was neutralized with a 1M hydrochloric acid solution (11.1 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}acrylic acid (1.79 g, yield: 69%) as colorless crystals. melting point 144-146°C.

Reference Example 322

To a mixture of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-3-isopropoxypropoxy)phenyl]acrylate (3.15 g), tetrahydrofuran (10 ml), and ethanol (10 ml) was added a 1M sodium hydroxide solution (12.5 ml), and the mixture was stirred at 50°C for 3 hr. The reaction mixture was poured into water, and the mixture was neutralized with a 1M hydrochloric acid solution (12.6 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-3-isopropoxypropoxy)phenyl]acrylic acid (2.18 g, yield: 73%) as colorless crystals. melting point 92-93°C.

Reference Example 323

A mixture of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-3-isopropoxypropoxy)phenyl]acrylic acid (772 mg), pyridine (0.014 ml), and acetic anhydride (4 ml) was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:1, v/v). The obtained oil was dissolved in tetrahydrofuran (20 ml), saturated aqueous sodium hydrogen carbonate (10 ml) was added, and the mixture was stirred at room temperature for 24 hr. The reaction mixture was concentrated, a 1M hydrochloric acid solution was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-(4-[2-(acetyloxy)-3-isopropoxypropoxy]-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylic acid (441 mg, yield: 53%) as colorless crystals. melting point 134-135°C.

Reference Example 324

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To a mixture of 5-methyl-1H-pyrrole-2-carbaldehyde (2.00 g), 2,4-dichlorobenzyl chloride (3.95 g) and N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 806 mg) at 0°C, and the mixture was stirred at 0°C for 1 hr and at room temperature for 8 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:10 - 1:4, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give 1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrrole-2-carbaldehyde (4.35 g, yield: 89%) as pale-yellow crystals. melting point 86-87°C.

Reference Example 325

A mixture of 1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrrole-2-carbaldehyde (3.76 g), malonic acid (5.84 g), piperidine (3.46 ml) and pyridine (25 ml) was stirred at 110°C for 8 hr. After cooling to room temperature, the reaction mixture was concentrated. A 1M hydrochloric acid solution was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrrol-2-yl]acrylic acid (2.51 g, yield: 58%) as yellow crystals. melting point 181-182°C.

Reference Example 326

To a mixture of 3,5-dimethyl-1H-pyrrole-2-carbaldehyde (3.30 g), 2,4-dichlorobenzyl chloride (5.76 g), and N,N-dimethylformamide (30 ml) was added sodium hydride (60% in oil, 1.18 g) at 0°C, and the mixture was stirred at 0°C for 1 hr and at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was

subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:10 - 1:5, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give 1-(2,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrrole-2-carbaldehyde (5.16 g, yield: 65%) as yellow crystals. melting point 88-89°C.

Reference Example 327

A mixture of 1-(2,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrrole-2-carbaldehyde (5.71 g), malonic acid (8.41 g), piperidine (4.99 ml), and pyridine (30 ml) was stirred at 110°C for 10 hr. After cooling to room temperature, and the reaction mixture was concentrated. A 1M hydrochloric acid solution was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5 - 1:1, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrrol-2-yl]acrylic acid (914 mg, yield: 14%) as yellow crystals. melting point 193-194°C.

Reference Example 328

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methoxymethoxy)-1,1-dimethylpropoxy]phenyl}-N-(pentylsulfonyl)acrylamide (111 mg) in acetone (3 ml) was added 1N hydrochloric acid (2 ml), and the mixture was stirred at 50°C for 6 hr. After allowing to cool to room temperature, a saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)-N-(pentylsulfonyl)acrylamide hemihydrate (69 mg, yield: 78%) as white crystals. melting point 80-83°C.

Reference Example 329

A mixture of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzaldehyde (1.00 g), malonic acid (280 mg), pyrrolidine (0.225 ml) and acetic acid (5 ml) was stirred at 100°C for 4.5 hr, and cooled to room temperature. 1N Hydrochloric acid (2 ml) and water (20 ml) were successively added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration, washed twice with water (20 ml) and air-dried. Diisopropyl ether-hexane (1:1, v/v, 10 ml) was added to the obtained yellow powder, and the mixture was stirred for 1 hr. The crystals were collected by filtration, washed three times with diisopropyl ether-hexane (1:1, v/v, 10 ml) and dried to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (989 mg, yield: 88%) as pale-yellow crystals.

Reference Example 330

To a solution of ethyl (2E)-3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]acrylate (2.50 g) in N,N-dimethylformamide (20 ml) were added 2,5-dibromo-3-methyl-6-pyridine (3.06 g) and potassium carbonate (3.24 g), and the mixture was stirred at 100°C for 72 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate- hexane (1:3, v/v) to give ethyl (2E)-3-[2-[(5-bromo-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (2.16 g, yield: 52%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.28 (3 H, t, J = 7.1 Hz), 2.38 (3 H, s), 3.42 (3 H, s), 3.71 - 3.74 (2 H, m), 4.09 - 4.12 (2 H, m), 4.19 (2 H, q, J = 7.1 Hz), 6.33 (1 H, d, J = 16.0 Hz), 6.59 (1 H, d, J = 2.6 Hz), 6.81 (1 H, dd, J = 8.8, 2.6 Hz), 7.60 (1 H,

d, J = 8.8 Hz), 7.66 - 7.67 (1 H, m), 7.76 (1 H, d, J = 16.0 Hz), 7.99 (1 H, d, J = 1.9 Hz).

Reference Example 331

To a mixed solution of ethyl (2E)-3-[2-[(5-bromo-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (880 mg) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added a 1N aqueous sodium hydroxide solution (4.0 ml), and the mixture was stirred at 60°C for 1 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethyl acetate -hexane to give (2E)-3-[2-[(5-bromo-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (785 mg, yield: 95%) as colorless crystals. melting point 157.0-157.9°C.

Reference Example 332

To a solution of 2-[(3,5-dichloropyridin-2-yl)oxy]-4-(3-methoxypropoxy)benzaldehyde (1.50 g) in tetrahydrofuran (15 ml) were added methyl methoxyacetate (0.97 g) and sodium tert-butoxide (1.05 g), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give methyl (2Z)-3-[2-hydroxy-4-(3-methoxypropoxy)phenyl]-2-methoxyacrylate (870 mg, yield: 69%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.00 - 2.05 (2 H, m), 3.35 (3 H, s), 3.54 (2 H, t, J = 6.1 Hz), 3.78 (3 H, s), 3.86 (3 H, s), 4.06 (2 H, t, J = 6.1 Hz), 6.45 - 6.48 (2 H, m), 7.09 (1 H, d, J = 9.6 Hz), 7.14 (1 H, s), 9.08 (1 H, s).

Reference Example 333

To a solution of methyl (2Z)-3-[2-hydroxy-4-(3-methoxypropoxy)phenyl]-2-methoxyacrylate (836 mg) in N,N-dimethylformamide (8 ml) were added 2,3-dichloro-5-(trifluoromethyl)pyridine (920 mg) and potassium carbonate (780 mg), and the mixture was stirred at 80°C for 5 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate- hexane (1:4, v/v) to give methyl (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-2-methoxyacrylate (1.25 g, yield: 93%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.00 - 2.05 (2 H, m), 3.34 (3 H, s), 3.53 (2 H, t, J = 6.0 Hz), 3.73 (3 H, s), 3.77 (3 H, s), 4.07 (2 H, t, J = 6.0 Hz), 6.68 (1 H, s), 6.88 (1 H, dd, J = 8.9, 2.6 Hz), 7.04 (1 H, s), 8.00 (1 H, d, J = 2.6 Hz), 8.22 (1 H, d, J = 8.9 Hz), 8.25 - 8.26 (1 H, m).

Reference Example 334

To a mixed solution of methyl (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-2-methoxyacrylate (1.07 g) in tetrahydrofuran (4 ml) and methanol (4 ml) was added a 1N aqueous sodium hydroxide solution (4.5 ml), and the mixture was stirred at 60°C for 1 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-

methoxypropoxy)phenyl]-2-methoxyacrylic acid (582 mg, yield: 56%) as colorless crystals. melting point 153.0-153.5°C.

Reference Example 335

To a solution of ethyl 3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]propanoate (4.84 g) in toluene (50 ml) was added a 1.5 M diisobutylaluminum hydride solution in toluene (16.0 ml) at 0°C, and the mixture was stirred at 0°C for 5 hr. Methanol and Celite were added to the reaction mixture, and the mixture was stirred for 30 min. Celite was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3, v/v) to give 3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]propan-1-ol (3.35 g, yield: 78%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.54 (1 H, s), 1.78 - 1.86 (2 H, m), 2.69 (2 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.54 - 3.60 (2 H, m), 3.71 - 3.74 (2 H, m), 4.07 - 4.10 (2 H, m), 5.02 (2 H, s), 6.46 (1 H, dd, J = 8.3, 2.3 Hz), 6.58 (1 H, d, J = 2.3 Hz), 7.05 (1 H, d, J = 8.3 Hz), 7.30 - 7.50 (5 H, m).

Reference Example 336

To a solution of 3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]propan-1-ol (1.01 g) in tetrahydrofuran (15 ml) was added N,N'-carbonyldiimidazole (780 mg), and the mixture was stirred at room temperature for 2 hr. (Aminomethyl)cyclopropane (475 mg) was added to the reaction mixture, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was concentrated, the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7, v/v) to give 3-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]propyl (cyclopropylmethyl)carbamate as a colorless amorphous solid (1.20 g). The obtained amorphous solid was dissolved in methanol (100 ml), 10% palladium-carbon (130 mg) was added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hr. The catalyst was filtered off, and

the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]propyl (cyclopropylmethyl)carbamate (940 mg, yield: 99%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.16 - 0.22 (2 H, m), 0.48 - 0.53 (2 H, m), 0.91 - 0.99 (1 H, m), 1.86 - 1.95 (2 H, m), 2.61 (2 H, t, J = 7.3 Hz), 3.02 - 3.07 (2 H, m), 3.44 (3 H, s), 3.71 - 3.74 (2 H, m), 4.05 - 4.11 (4 H, m), 4.76 - 4.83 (1 H, m), 5.59 (1 H, s), 6.41 - 6.46 (2 H, m), 6.97 (1 H, d, J = 8.1 Hz).

Reference Example 337

Under ice-cooling, to a mixture of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)benzaldehyde (10.0 g), triethyl 2-phosphonopropionate (7.24 g), tetrahydrofuran (30 ml) and N,N-dimethylformamide (30 ml) was added lithium hydroxide monohydrate (1.28 g), and the mixture was stirred for 2 hr. 0.1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give a mixture (11.4 g) of ethyl (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]-2-methylacrylate and ethyl (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]-2-methylacrylate.

To a solution of the obtained mixture (5.00 g) in ethanol (50 ml) was added concentrated hydrochloric acid (2.5 ml), and the mixture was stirred at 50°C for 5 hr. The reaction mixture was concentrated, and the residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 3:7, v/v), concentrated, and crystallized from ethyl

acetate-hexane to give ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)-2-methylacrylate (3.04 g, 73%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.26 (3 H, t, J = 7.2 Hz), 2.01 (3 H, d, J = 1.5 Hz), 4.17 (2 H, q, J = 7.0 Hz), 5.11 (1 H, s), 6.72 (1 H, d, J = 2.4 Hz), 6.80 (1 H, dd, J = 8.5, 2.4 Hz), 7.35 (1 H, d, J = 8.5 Hz), 7.50 (1 H, d, J = 1.3 Hz), 7.97 (1 H, d, J = 2.3 Hz), 8.24 (1 H, dd, J = 2.1, 1.1 Hz).

Reference Example 338

To a solution of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)-2-methylacrylate (3.00 g) in N,N-dimethylformamide (50 ml) were added isopropyliodide (1.50 ml) and potassium carbonate (4.12 g), and the mixture was stirred at 50°C for 2 hr. The reaction mixture was filtrated, ethyl acetate was added to the filtrate. The mixture was washed successively with saturated brine and water, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 2:8, v/v), concentrated, and crystallized from ethyl acetate-hexane to give ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylate (3.17 g, 96%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.25 (3 H, t, J = 7.1 Hz), 1.36 (6 H, d, J = 6.0 Hz), 1.96 - 2.09 (3 H, m), 4.02 - 4.27 (2 H, m), 4.42 - 4.67 (1 H, m), 6.72 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.6, 2.4 Hz), 7.39 (1 H, d, J = 8.7 Hz), 7.51 (1 H, s), 7.96 (1 H, d, J = 2.1 Hz), 8.23 (1 H, d, J = 0.9 Hz).

Reference Example 339

To a mixture of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylate (3.00 g), ethanol (20 ml), tetrahydrofuran (10 ml) and water (10 ml) was added lithium hydroxide monohydrate (2.27 g), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was acidified with 1N hydrochloric

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acid, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 2:8, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (2.00 g, 71%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.36 (6 H, d, J = 6.0 Hz), 2.05 (3 H, d, J = 1.5 Hz), 4.48 - 4.64 (1 H, m), 6.70 (1 H, d, J = 2.4 Hz), 6.85 (1 H, dd, J = 8.7, 2.4 Hz), 7.41 (1 H, d, J = 8.7 Hz), 7.64 (1 H, s), 7.97 (1 H, d, J = 1.9 Hz), 8.19 - 8.28 (1 H, m).

Reference Example 340

To a solution of benzyl alcohol (2.00 g) in acetonitrile (100 ml) was added chlorosulfonylisocyanate (2.75 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (5.3 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-(Aminoethyl)-5-methylpyrazine (11.4 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:8 - 1:0, v/v), concentrated, and crystallized from ethyl acetate-hexane to give benzyl ({[(5-methylpyrazin-2-yl)methyl]amino}sulfonyl)carbamate (3.27 g, 53%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.55 (3 H, s), 4.38 - 4.49 (2 H, m), 5.15 (2 H, s), 6.06 (1 H, br.s.), 7.32 - 7.47 (6 H, m), 8.30 (1 H, s), 8.46 (1 H, s).

Reference Example 341

To a solution of benzyl alcohol (2.00 g) in acetonitrile (100 ml) was added chlorosulfonylisocyanate (2.75 g) under

ice-cooling, and the mixture was stirred for 30 min. Pyridine (5.3 ml) was added to the reaction mixture, the mixture was stirred for 1 hr, 2-(2-aminoethyl)pyridine (11.3 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with methanol-ethyl acetate (0:1 - 1:0, v/v) and concentrated to give benzyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (4.58 g, 74%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.03 (2 H, t, J = 6.3 Hz), 3.44 - 3.55 (2 H, m), 5.12 (2 H, s), 7.08 - 7.18 (2 H, m), 7.32 (5 H, s), 7.55 - 7.66 (1 H, s), 8.40 - 8.48 (1 H, m).

Reference Example 342

To a solution of benzyl alcohol (2.00 g) in acetonitrile (100 ml) was added chlorosulfonylisocyanate (2.75 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (5.3 ml) was added to the reaction mixture, the mixture was stirred for 1 hr, 2-(2-aminoethyl)pyridine (11.3 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give benzyl (pyrrolidin-1-ylsulfonyl)carbamate (2.99 g, 54%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.80 - 1.96 (4 H, m), 3.41 - 3.54 (4 H, m), 5.17 (2 H, s), 7.16 (1 H, br.s.), 7.32 - 7.43 (5 H, s).

Reference Example 343

A suspension of benzyl ({[(5-methylpyrazin-2-yl)methyl]amino}sulfonyl)carbamate (3.00 g) and 10% palladium-

carbon (0.30 g) in methanol (80 ml) was stirred under a hydrogen atmosphere at room temperature for 6 hr. The reaction mixture was filtrated, and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, eluted with methanol-ethyl acetate (0:1 - 2:8, v/v), concentrated and crystallized from ethyl acetate-hexane to give N-[(5-methylpyrazin-2-yl)methyl]sulfamide (1.29 g, 72%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.59 (3 H, s), 4.47 (2 H, s), 4.68 (2 H, br.s.), 5.33 (1 H, br.s.), 8.41 (1 H, s), 8.50 (1 H, s).

Reference Example 344

A suspension of benzyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (4.58 g) and 10% palladium-carbon (0.46 g) in ethanol (100 ml) was stirred under a hydrogen atmosphere at room temperature for 6 hr. The reaction mixture was filtrated, and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, eluted with methanol-ethyl acetate (0:1 - 1:0, v/v) and concentrated to give N-(2-pyridin-2-ylethyl)sulfamide (1.46 g, 53%) as a colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.94 (2 H, t, J = 7.6 Hz), 3.16 - 3.29 (2 H, m), 6.41 - 6.69 (3 H, m), 7.13 - 7.34 (2 H, m), 7.62 - 7.78 (1 H, m), 8.49 (1 H, d, J = 4.5 Hz).

Reference Example 345

A suspension of benzyl (pyrrolidin-1-ylsulfonyl)carbamate (2.50 g) and 10% palladium-carbon (0.30 g) in ethanol (80 ml) was stirred under a hydrogen atmosphere at room temperature for 6 hr. The reaction mixture was filtrated, and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give pyrrolidine-1-sulfonamide (1.04 g, 79%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.81 - 2.02 (4 H, m), 3.19 - 3.37 (4 H, m), 4.50 (2 H, br.s.).

Reference Example 346

A mixture of ethyl (2E)-3-(2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (11.4 g), platinum (IV) oxide (133 mg), and ethanol-tetrahydrofuran (292 ml, v/v=1/1) was stirred under a hydrogen atmosphere at room temperature for 6 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v) to give ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (10.8 g, yield: 94%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.14 - 1.31 (3 H, m), 2.57 (2 H, t, J = 7.6 Hz), 2.75 (2 H, t, J = 7.7 Hz), 4.02 - 4.18 (2 H, m), 5.48 (1 H, d, J = 7.0 Hz), 6.59 (1 H, d, J = 2.4 Hz), 6.68 (1 H, dd, J = 8.3, 2.4 Hz), 7.17 (1 H, d, J = 8.3 Hz), 7.99 (1 H, s), 8.27 (1 H, s).

Reference Example 347

To a mixture of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (1.01 g), 1-butanol (0.29 g), tributylphosphine (1.05 g) and tetrahydrofuran (10 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.31 g) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:9 - 3:7, v/v) to give ethyl 3-(4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate (1.1 g, yield: 95%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.96 (3 H, t, J = 7.4 Hz), 1.21 (3 H, t, J = 7.2 Hz), 1.37 - 1.81 (4 H, m), 2.52 - 2.61 (2 H, m), 2.70 - 2.80 (2 H, m), 3.87 - 3.97 (2 H, m), 4.03 - 4.15 (2 H, m), 6.64 (1 H, d, J = 2.6 Hz), 6.78 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.27 (1 H, d, J = 1.1 Hz).

Reference Example 348

Ethyl 3-(4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate (1.1 g) was dissolved in diethyl ether (5 ml), a 1.5 M solution (4.1 ml) of diisobutylaluminum hydride in toluene was added at 0°C, and the mixture was stirred at room temperature for 1.5 hr. Methanol and water were added to the reaction mixture, and the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 2:3, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-(4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propan-1-ol (0.69 g, yield: 69%) as colorless crystals. melting point 72.6-72.7°C.

Reference Example 349

To a solution of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (1.03 g) in N,N-dimethylformamide (5.3 ml) were added 1-bromo-3-methoxypropane (0.60 g), potassium carbonate (0.73 g) and sodium iodide (0.80 g), and the mixture was stirred at 80°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:17 - 2:3, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propanoate (0.84 g, yield: 69%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.0 Hz), 1.98 - 2.08 (2 H, m), 2.56 (2 H, t, J = 7.8 Hz), 2.76 (2 H, t, J = 7.6 Hz), 3.34 (3 H, s), 3.53 (2 H, t, J = 6.1 Hz), 3.96 - 4.14 (4 H, m), 6.65 (1 H, d, J = 2.7 Hz), 6.79 (1 H, dd, J = 8.5, 2.5 Hz), 7.22 (1 H, d, J = 8.3 Hz), 7.98 (1 H, d, J = 2.3 Hz), 8.27 (1 H, s).

Reference Example 350

Ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propanoate (840 mg) was dissolved in diethyl ether (3.6 ml), a 1.5 M diisobutylaluminum hydride toluene solution (3.0 ml) was added at 0°C, and the mixture was stirred at room temperature for 2.5 hr. Methanol and water were added to the reaction mixture, and the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 1:1, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propan-1-ol (665 mg, yield: 87%) as colorless crystals. melting point 68.7-70.9°C.

Reference Example 351

To a solution of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (1.03 g) in N,N-dimethylformamide (5.3 ml) was added sodium hydride (60% in oil, 0.15 g), and the mixture was stirred at 0°C for 30 min. Further, 4-bromo-1-butene (0.53 g) was added, and the mixture was stirred at 50°C for 48 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:7, v/v) to give ethyl 3-(4-(but-3-en-1-yloxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate (0.68 g, yield: 58%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.1 Hz), 2.47 - 2.61 (4 H, m), 2.76 (2 H, t, J = 7.6 Hz), 3.95 - 4.01 (2 H, m), 4.04 - 4.13 (2 H, m), 5.06 - 5.20 (2 H, m), 5.80 - 5.96 (1 H, m), 6.65 (1 H, d, J = 2.6 Hz), 6.79 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.27 (1

H, d, J = 1.1 Hz).

Reference Example 352

Ethyl 3-(4-(but-3-en-1-yloxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate (683 mg) was dissolved in diethyl ether (3.0 ml), a 1.5 M solution (2.6 ml) of diisobutylaluminum hydride in toluene was added at 0°C, and the mixture was stirred at room temperature for 4 hr. Methanol and water were added to the reaction mixture, and the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 2:3, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-(4-(but-3-en-1-yloxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propan-1-ol (525 mg, yield: 85%) as colorless crystals. melting point 75.2-75.8°C.

Reference Example 353

To a mixture of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (1.09 g), 2-furylmethanol (0.41 g), tributylphosphine (1.14 g) and tetrahydrofuran (11 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.42 g) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-furylmethoxy)phenyl]propanoate (1.05 g, yield: 80%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.17 - 1.24 (3 H, m), 2.53 - 2.62 (2 H, m), 2.78 (2 H, t, J = 7.6 Hz), 4.04 - 4.15 (2 H, m), 4.96 (2 H, s), 6.35 - 6.43 (2 H, m), 6.74 (1 H, d, J = 2.6 Hz), 6.87 (1 H, dd, J = 8.5, 2.6 Hz), 7.21 - 7.27 (1 H, m), 7.41 - 7.46 (1

H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.3, 0.9 Hz).

Reference Example 354

Ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-furylmethoxy)phenyl]propanoate (1050 mg) was dissolved in diethyl ether (4.5 ml), a 1.5 M solution (3.7 ml) of diisobutylaluminum hydride in toluene was added at 0°C, and the mixture was stirred at room temperature for 2.5 hr. Methanol and water were added to the reaction mixture, and the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 2:3, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-furylmethoxy)phenyl]propan-1-ol (734 mg, yield: 77%) as colorless crystals. melting point 68.0-68.6°C.

Reference Example 355

To a mixture of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (1.09 g), 4-(2-hydroxyethyl)morpholine (0.55 g), tributylphosphine (1.13 g) and tetrahydrofuran (11 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.41 g) at room temperature, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:1 - 7:3, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-morpholin-4-ylethoxy)phenyl]propanoate (1.14 g, yield: 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.17 - 1.30 (3 H, m), 2.52 - 2.61 (6 H, m), 2.72 - 2.82 (4 H, m), 3.69 - 3.75 (4 H, m), 4.04 - 4.16 (4 H, m), 6.67 (1 H, d, J = 2.6 Hz), 6.79 (1 H, dd, J = 8.5,

2.6 Hz), 7.23 (1 H, d, J = 8.5 Hz), 7.99 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Reference Example 356

Ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-morpholin-4-ylethoxy)phenyl]propanoate (1139 mg) was dissolved in diethyl ether (4.5 ml), a 1.5 M solution (3.8 ml) of diisobutylaluminum hydride in toluene was added at 0°C, and the mixture was stirred at room temperature for 2.5 hr. Methanol and water were added to the reaction mixture, and the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-morpholin-4-ylethoxy)phenyl]propan-1-ol (737 mg, yield: 71%) as colorless crystals. melting point 69.2-70.4°C.

Reference Example 357

To a mixture of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (1.05 g), tetrahydrofurfuryl alcohol (0.41 g), tributylphosphine (1.09 g) and tetrahydrofuran (10 ml) was added 1,1'-(azodicarbonyl)dipiperidine (1.36 g) at room temperature, and the mixture was stirred for 20 hr. The reaction mixture was concentrated, diisopropyl ether was added, and the precipitated crystals were filtered off. The filtrate was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (3:17 - 1:4, v/v) to give ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]propanoate (789 mg, yield: 62%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 1.86 - 2.17 (4 H, m), 2.52 - 2.61 (2 H, m), 2.76 (2 H, t, J = 7.7 Hz), 3.75 - 3.96 (4 H, m), 4.04 - 4.14 (2 H, m), 4.22 - 4.30 (1 H, m), 6.68 (1 H, d, J = 2.6 Hz), 6.81 (1 H, dd, J = 8.5, 2.6 Hz),

7.22 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Reference Example 358

Ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]propanoate (739 mg) was dissolved in diethyl ether (3.0 ml), a 1.5 M solution (2.6 ml) of diisobutylaluminum hydride in toluene was added at 0°C, and the mixture was stirred at room temperature for 3 hr. Methanol and water were added to the reaction mixture, and the mixture was stirred for a while, filtered through celite, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 2:3, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]propan-1-ol (495 mg, yield: 73%) as colorless crystals. melting point 91.3-93.6°C.

Reference Example 359

A suspension of ethyl (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylate (12.1 g) and 10% palladium-carbon (1.21 g) in ethanol (250 ml) was stirred under a hydrogen atmosphere at room temperature for 6 hr. The reaction mixture was filtrated, and the solvent was evaporated under reduced pressure to give ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)propanoate (12.1 g, quant.) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.00 - 1.10 (21 H, m), 1.21 (3 H, t, J = 7.2 Hz), 2.47 - 2.64 (2 H, m), 2.76 (2 H, t, J = 7.8 Hz), 3.86 - 4.21 (6 H, m), 6.67 (1 H, d, J = 2.6 Hz), 6.76 - 6.87 (1 H, m), 7.22 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.26 (1 H, d, J = 1.1 Hz).

Reference Example 360

To a solution of ethyl 3-(2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)propanoate (12.1 g) in diethyl ether (50 ml) was added dropwise a 1.5 M solution (34.3 ml) of diisobutylaluminum hydride in toluene, and the mixture was stirred while warming to room temperature over 4 hr. Saturated brine was added to the reaction mixture, the mixture was filtrated, and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 2:8, v/v) and concentrated to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)propan-1-ol (8.74 g, 77%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.98 - 1.19 (21 H, m), 1.37 (1 H, t, J = 5.7 Hz), 1.73 - 1.92 (2 H, m), 2.49 - 2.57 (2 H, m), 3.60 (2 H, q, J = 6.2 Hz), 4.01 - 4.04 (4 H, m), 6.66 (1 H, d, J = 2.4 Hz), 6.77 - 6.88 (1 H, m), 7.22 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Example 1

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (3.49 g) in tetrahydrofuran (40 ml) was added N,N'-carbonyldiimidazole (2.08 g), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (1.63 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:1, v/v) to give a white solid.

Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide (1.62 g, yield: 35%) as white feather crystals. melting point 140-142°C.

Example 2

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propionic acid (530 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (313 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (225 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-(pentylsulfonyl)propanamide (353 mg, yield: 50%) as white feather crystals. melting point 94-95°C. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.94 (3 H, m), 1.24 - 1.41 (10 H, m), 1.60 - 1.73 (2 H, m), 2.55 (2 H, t, J = 7.2 Hz), 2.96 (2 H, t, J = 7.1 Hz), 3.12 - 3.20 (2 H, m), 4.36 - 4.55 (1 H, m), 6.45 (1 H, d, J = 2.4 Hz), 6.74 (1 H, dd, J = 8.4, 2.5 Hz), 7.17 (1 H, d, J = 8.5 Hz), 8.08 (1 H, d, J = 2.1 Hz), 8.33 - 8.43 (1 H, m).

Recrystallization of the crude crystals obtained under the same conditions as in Example 2 from ethyl acetate-hexane gave crystals. The X-ray powder diffraction pattern of this crystal as measured using Cu-Kα ray (tube voltage: 40 KV; tube

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current: 50 mA) as a radiation source and RINT2100 type Ultima+ (Rigaku Corporation) is shown in Fig. 1.

Data (main peak) of X-ray powder diffraction

diffraction angle: 2θ (°) spacing: d value (angstrom))

6.50	13.6
12.8	6.90
16.4	5.39
17.2	5.15
19.5	4.54
22.1	4.01
22.7	3.91
24.2	3.67

Example 3

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (502 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (213 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, benzenesulfonamide (212 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:4, v/v) to give a colorless oil. This was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-methanol (ethyl acetate alone to 4:1, v/v) and then with 2.0 M ammonia methanol solution to give a yellow oil. The obtained oil was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]-N-(phenylsulfonyl)propanamide (338 mg, yield: 51%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.46 (2 H, t, J = 7.2 Hz), 2.84 (2 H, t, J = 7.1 Hz), 3.44 (3 H, s), 3.73 (2 H, dd, J = 5.4, 3.9 Hz), 4.04 (2 H, dd, J = 5.4, 3.9 Hz), 6.33 - 6.46 (2 H, m), 6.78 (1 H, d, J = 8.5 Hz), 7.44 - 7.55 (1 H, m), 7.60 - 7.69 (1 H, m), 7.82 - 7.89 (2 H, m), 8.08 (1 H, d, J = 1.9 Hz), 8.42 - 8.51 (1 H, m), 9.39 (1 H, s).

Example 4

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propionic acid (1.47 g) in tetrahydrofuran (20 ml) were added thionyl chloride (0.75 ml) and N,N-dimethylformamide (0.10 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (20 ml). Benzenesulfonamide (685 mg), N,N-diisopropylethylamine (0.80 ml) and 4-dimethylaminopyridine (431 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for 3 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:2, v/v) to give a pale-yellow oil. This was dissolved in a suspension of activated carbon in ethyl acetate, the mixture was stirred at room temperature for 30 min, filtrated and concentrated to give a pale-yellow solid. Recrystallization from ethyl acetate-hexane gave 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-(phenylsulfonyl)propanamide (1.02 g, yield: 52%) as white crystals. melting point 129.0-129.5°C.

Example 5

To a solution of 3-[2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (114 mg) in tetrahydrofuran (2 ml) were added thionyl chloride (0.05 ml) and N,N-dimethylformamide (0.01 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (2 ml). 4-Chlorobenzenesulfonamide (60 mg), N,N-diisopropylethylamine (0.05 ml) and 4-dimethylaminopyridine (39 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for 3 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give N-[(4-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanamide (88 mg, yield: 54%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 140-141.5°C.

Example 6

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (140 mg) in tetrahydrofuran (2 ml) were added thionyl chloride (0.05 ml) and N,N-dimethylformamide (0.01 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (2 ml). p-Toluenesulfonamide (65 mg), N,N-diisopropylethylamine (0.10 ml) and 4-dimethylaminopyridine (42 mg) were added to the reaction mixture at room temperature, and 30 min later, N,N-diisopropylethylamine (0.10 ml) was added. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted

with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give a pale-yellow oil. The obtained oil was mixed with an excess amount of triethylamine, and an excess amount of the reagent was evaporated under reduced pressure. The obtained mixture was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 4:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(4-methylphenyl)sulfonyl]propanamide (23 mg, 12%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.42 - 2.51 (2 H, m), 2.83 (2 H, t, J = 7.3 Hz), 3.44 (3 H, s), 3.70 - 3.77 (2 H, m), 4.00 - 4.11 (2 H, m), 6.40 - 6.49 (2 H, m), 6.82 (1 H, d, J = 9.1 Hz), 7.22 - 7.35 (2 H, m), 7.72 (2 H, d, J = 8.5 Hz), 8.06 (1 H, d, J = 2.2 Hz), 8.42 (1 H, s).

Example 7

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (169 mg) in tetrahydrofuran (2 ml) were added thionyl chloride (0.05 ml) and N,N-dimethylformamide (0.01 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (2 ml). 4-Methoxybenzenesulfonamide (85 mg), N,N-diisopropylethylamine (0.10 ml) and 4-dimethylaminopyridine (62 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for 80 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and

eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give a colorless oil. This was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-methanol (ethyl acetate alone to 4:1, v/v), then with a 2.0 M ammonia methanol solution to give a red solid. The obtained solid was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(4-methoxyphenyl)sulfonyl]propanamide (125 mg, yield: 53%) as a colorless solid. Recrystallization from ethyl acetate-hexane gave a white powder. melting point 118-120°C.

Example 8

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (494 mg) in tetrahydrofuran (5 ml) were added thionyl chloride (0.15 ml) and N,N-dimethylformamide (0.05 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (5 ml). 2-Chlorobenzenesulfonamide (245 mg), N,N-diisopropylethylamine (0.40 ml) and 4-dimethylaminopyridine (167 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 1:1, v/v) to give a colorless oil. The obtained oil was mixed with an excess amount of triethylamine, and an excess amount of the reagent was evaporated under reduced pressure. The obtained mixture was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 4:1, v/v) to give N-[(2-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]propanamide (608 mg, 87%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (2 H, t, J = 7.3 Hz), 2.78 (2 H, t, J = 7.3 Hz), 3.43 (3 H, s), 3.70 - 3.76 (2 H, m), 4.01 - 4.10 (2 H, m), 6.56 (1 H, d, J = 2.5 Hz), 6.68 (1 H, dd, J = 8.5, 2.5 Hz), 7.03 (1 H, d, J = 8.5 Hz), 7.38 - 7.48 (2 H, m), 7.49 - 7.59 (1 H, m), 8.00 (1 H, d, J = 2.2 Hz), 8.20 (1 H, dd, J = 7.8, 1.8 Hz), 8.33 (1 H, d, J = 1.4 Hz).

Example 9

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (515 mg) in tetrahydrofuran (5 ml) were added thionyl chloride (0.15 ml) and N,N-dimethylformamide (0.05 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (5 ml). o-Toluenesulfonamide (221 mg), N,N-diisopropylethylamine (0.40 ml) and 4-dimethylaminopyridine (140 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 1:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(2-methylphenyl)sulfonyl]propanamide (171 mg, yield: 24%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.37 (3 H, s), 2.50 (2 H, t, J = 7.2 Hz), 2.82 (2 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.68 - 3.79 (2 H, m), 4.03 - 4.10 (2 H, m), 6.45 - 6.62 (2 H, m), 6.88 (1 H, d, J = 8.5 Hz), 7.22 - 7.27 (1 H, m), 7.30 - 7.39 (1 H, m), 7.44 - 7.57 (1 H, m), 7.97 - 8.11 (2 H, m), 8.42 (1 H, d, J = 1.1 Hz), 9.19 (1 H, s).

Example 10

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (498 mg) in tetrahydrofuran (5 ml) were added thionyl chloride (0.15 ml) and N,N-dimethylformamide (0.05 ml) under ice-cooling, and the mixture was stirred for 3 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran (5 ml). 4-Ethylbenzenesulfonamide (249 mg), N,N-diisopropylethylamine (0.40 ml) and 4-dimethylaminopyridine (158 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 1:1, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl}oxy}-4-(2-methoxyethoxy)phenyl]-N-[(4-ethylphenyl)sulfonyl]propanamide (157 mg, yield: 23%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.7 Hz), 2.45 (2 H, t, J = 7.1 Hz), 2.69 - 2.89 (4 H, m), 3.44 (3 H, s), 3.70 - 3.76 (2 H, m), 4.02 - 4.07 (2 H, m), 6.39 - 6.52 (2 H, m), 6.82 (1 H, d, J = 8.0 Hz), 7.28 - 7.36 (2 H, m), 7.70 - 7.81 (2 H, m), 8.06 (1 H, d, J = 2.2 Hz), 8.37 - 8.49 (1 H, m), 9.21 (1 H, s).

Example 11

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (496 mg) in tetrahydrofuran (5 ml) were added thionyl chloride (0.15 ml) and N,N-dimethylformamide (0.05 ml) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated, and the residue was dissolved in tetrahydrofuran

(5 ml). 4-Fluorobenzenesulfonamide (225 mg), N,N-diisopropylethylamine (0.40 ml) and 4-dimethylaminopyridine (140 mg) were added to the reaction mixture at room temperature, and the mixture was stirred for overnight. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 1:1, v/v) to give a white solid. The obtained solid was mixed with an excess amount of triethylamine, and an excess amount of the reagent was evaporated under reduced pressure. The obtained mixture was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1 - 9:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(4-fluorophenyl)sulfonyl]propanamide (105 mg, yield: 15%) as a white powder. melting point 136-138°C.

Example 12

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (2.31 g) in tetrahydrofuran (50 ml) was added N,N'-carbonyldiimidazole (1.37 g), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (1.02 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.80 ml) were added to the reaction mixture, and the mixture was stirred for 3 hr. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl

acetate-hexane (1:9 - 1:4, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (493 mg, yield: 16%) as white crystals. melting point 127-130°C. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (3 H, t, J = 7.1 Hz), 1.24 - 1.48 (4 H, m), 1.83 (2 H, tt, J = 7.6, 7.6 Hz), 3.44 (3 H, s), 3.45 - 3.50 (2 H, m), 3.71 - 3.80 (2 H, m), 4.04 - 4.20 (2 H, m), 6.37 (1 H, d, J = 15.6 Hz), 6.70 (1 H, d, J = 2.4 Hz), 6.91 (1 H, dd, J = 8.7, 2.4 Hz), 7.60 (1 H, d, J = 8.9 Hz), 7.79 (1 H, d, J = 15.6 Hz), 7.87 (1 H, s), 8.03 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.2, 1.0 Hz).

Recrystallization of the crude crystals obtained under the same conditions as in Example 12 from ethanol gave crystals. The X-ray powder diffraction pattern of this crystal as measured using Cu-Kα ray (tube voltage: 40 KV; tube current: 50 mA) as a radiation source and RINT2100 type Ultima+ (Rigaku Corporation) is shown in Fig. 2.

Data (main peak) of X-ray powder diffraction

diffraction angle: 2θ (°)	spacing: d value (angstrom)
7.18	12.3
14.2	6.27
16.3	5.44
17.8	4.99
18.7	4.74
21.7	4.09
23.3	3.81
25.7	3.46
27.0	3.29

Example 13

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]acrylic acid (0.95 g) in tetrahydrofuran (20 ml) was added N,N'-carbonyldiimidazole (628 mg), and the mixture was heated under reflux for 1.5 hr. After cooling to room temperature, pentane-

1-sulfonamide (397 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]-N-(pentylsulfonyl)acrylamide (438 mg, yield: 35%) as white fine needles. melting point 142-144°C.

Example 14

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (79 mg) in acetonitrile (5 ml) was added benzenesulfonylisocyanate (105 mg), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 3:2, v/v) to give a white solid. The solid was recrystallized from ethyl acetate-hexane and the obtained solid was washed with acetonitrile, subjected to basic silica gel column chromatography and eluted with 2.0 M ammonia methanol solution to give a red solid. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give N-[({3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}amino)carbonyl]benzenesulfonamide (15 mg, yield: 13%, purity 90%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.67 - 1.86 (2 H, m), 2.43 (2 H, t, J = 7.6 Hz), 3.19 (2 H, d, J = 6.0 Hz), 3.43 (3 H, s), 3.73 (2

H, dd, J = 5.5, 4.0 Hz), 4.09 (2 H, dd, J = 5.4, 3.9 Hz), 6.57 (1 H, t, J = 5.6 Hz), 6.67 (1 H, t, J = 2.6 Hz), 6.81 (1 H, dd, J = 8.5, 2.6 Hz), 7.13 (1 H, d, J = 8.5 Hz), 7.40 - 7.53 (2 H, m), 7.60 (1 H, t, J = 7.5 Hz), 7.78 - 7.93 (2 H, m), 7.99 (1 H, d, J = 1.9 Hz), 8.25 (1 H, dd, J = 2.2, 1.0 Hz).

Example 15

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (492 mg) in ethyl acetate (20 ml) were added triethylamine (0.20 ml) and methanesulfonyl chloride (0.25 ml) and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a pale-orange solid. Recrystallization from ethyl acetate-hexane gave N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}methanesulfonamide (211 mg, yield: 36%) as white crystals. melting point 89-90°C.

Example 16

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (455 mg) in ethyl acetate (10 ml) were added pyridine (1.0 ml) and benzenesulfonyl chloride (0.15 ml), and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected

to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a colorless solid. Recrystallization from ethyl acetate-hexane gave N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}benzenesulfonamide (205 mg, yield: 34%) as white crystals. melting point 94-95°C.

Example 17

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (451.1 mg) in ethyl acetate (10 ml) were added pyridine (1.0 ml) and 2,4-dichlorobenzenesulfonyl chloride (301 mg), and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a pale-yellow solid. The obtained solid was subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give 2,4-dichloro-N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}benzenesulfonamide (236 mg, yield: 35%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.68 - 1.82 (2 H, m), 2.46 (2 H, t, J = 7.3 Hz), 2.75 - 2.96 (2 H, m), 3.44 (3 H, s), 3.65 - 3.78 (2 H, m), 4.00 - 4.15 (2 H, m), 4.99 (2 H, t, J = 6.1 Hz), 6.65 (1 H, d, J = 2.4 Hz), 6.80 (1 H, dd, J = 8.5, 2.4 Hz), 7.11 (1 H, d, J = 8.5 Hz), 7.37 (1 H, dd, J = 8.5, 1.9 Hz), 7.51 (1 H, d, J = 1.9 Hz), 7.90 - 8.03 (2 H, m), 8.25 (1 H, d, J = 0.9 Hz).

Example 18

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (1.01 g) in ethyl acetate (10 ml) were added pyridine (2.5 ml) and 1-pentanesulfonyl chloride (0.50 g), and the mixture was stirred at room temperature for 1.5 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}pentane-1-sulfonamide (198 mg, yield: 15%) as white crystals. melting point 87-90°C.

Example 19

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (289 mg) in ethyl acetate (10 ml) were added pyridine (5.0 ml) and phenylmethanesulfonyl chloride (182.1 mg), and the mixture was stirred at room temperature for 2.5 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-1-phenylmethanesulfonamide (75 mg, yield: 19%) as white crystals. melting point 97-100°C.

Example 20

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (505 mg) in ethyl acetate (10 ml) were added pyridine (0.5 ml) and cyclohexanesulfonyl chloride (362 mg), and the mixture was stirred at room temperature for 3.5 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}cyclohexanesulfonamide (53 mg, yield: 8%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.11 - 1.94 (10 H, m), 1.99 - 2.18 (2 H, m), 2.53 (2 H, t, J = 7.3 Hz), 2.66 - 2.94 (2 H, m), 3.08 (2 H, m), 3.44 (3 H, s), 3.68 - 3.80 (2 H, m), 3.96 - 4.15 (2 H, m), 6.67 (1 H, d, J = 2.6 Hz), 6.84 (1 H, dd, J = 8.5, 2.4 Hz), 7.20 (1 H, d, J = 8.5 Hz), 8.00 (1 H, d, J = 2.1 Hz), 8.27 (1 H, d, J = 0.8 Hz).

Example 21

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (196 mg) in ethyl acetate (10 ml) were added pyridine (0.5 ml) and 3-phenylpropanesulfonyl chloride (182 mg), and the mixture was stirred at room temperature for 1.5 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl

acetate-hexane (1:19 - 2:3, v/v) to give a white solid. The obtained solid was dissolved in a suspension of activated carbon in ethyl acetate, and the mixture was stirred for 3 hr, filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-3-phenylpropane-1-sulfonamide (75 mg, yield: 26%) as white crystals. melting point 101.8-102.0°C.

Example 22

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (234 mg) in ethyl acetate (10 ml) were added pyridine (5.0 ml) and 4-chlorobenzenesulfonyl chloride (185 mg), and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 35:65, v/v). Activated carbon was suspended in the eluted fraction, and the mixture was stirred for 1 hr, filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave 4-chloro-N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}benzenesulfonamide (145 mg, yield: 43%) as white feather crystals. melting point 111-113°C.

Example 23

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (275 mg) in ethyl acetate (10 ml) were added pyridine (5.0 ml) and 2-chlorobenzenesulfonyl chloride (227 mg), and the mixture was

stirred at room temperature for 6 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a pale-yellow oil. The obtained oil was dissolved in a suspension of activated carbon in ethyl acetate, and the mixture was stirred for 1 hr. The reaction mixture was filtrated and concentrated to give 2-chloro-N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}benzenesulfonamide (10 mg, yield: 3%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.63 - 1.81 (10 H, m), 2.46 (2 H, t, J = 7.3 Hz), 2.89 (2 H, q, J = 6.7 Hz), 3.43 (3 H, s), 3.69 - 3.76 (2 H, m), 4.01 - 4.12 (2 H, m), 5.00 (1 H, t, J = 6.0 Hz), 6.64 (1 H, d, J = 2.4 Hz), 6.79 (1 H, dd, J = 8.6, 2.5 Hz), 7.11 (1 H, d, J = 8.5 Hz), 7.30 - 7.45 (1 H, m), 7.50 (2 H, d, J = 3.8 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.06 (1 H, d, J = 7.7 Hz), 8.24 (1 H, s).

Example 24

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (150 mg) in ethyl acetate (10 ml) were added pyridine (5.0 ml) and 3-chlorobenzenesulfonyl chloride (191 mg), and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl

acetate-hexane gave 3-chloro-N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}benzenesulfonamide (40 mg, yield: 19%) as white feather crystals. melting point 110-114°C.

Example 25

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propane-1-amine (147 mg) in ethyl acetate (10 ml) were added pyridine (5.0 ml) and 2-propanesulfonyl chloride (122 mg), and the mixture was stirred at room temperature for 6 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v). Activated carbon was suspended in the eluted fraction, and the mixture was stirred for 1 hr. The reaction mixture was filtrated and concentrated to give N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}propane-2-sulfonamide (11 mg, yield: 6%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.8 Hz), 1.61 - 2.07 (2 H, m), 2.53 (2 H, t, J = 7.3 Hz), 2.88 - 2.99 (1 H, m), 3.01 - 3.22 (2 H, m), 3.38 - 3.48 (3 H, m), 3.64 - 3.76 (2 H, m), 3.95 - 4.17 (2 H, m), 6.67 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.20 (1 H, d, J = 8.5 Hz), 8.00 (1 H, s), 8.27 (1 H, d, J = 1.1 Hz).

Example 26

A solution of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylic acid (150 mg) and N,N'-carbonyldiimidazole (67 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To this mixture were added 3-methylbutane-1-sulfonamide (62 mg) and 1,8-

diazabicyclo[5.4.0]undec-7-ene (0.062 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:20 - 2:3, v/v) and concentrated. The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]acrylamide (124 mg, yield: 62%) as colorless crystals. melting point 155.5-157.5°C.

Example 27

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propen-1-ol (2.26 g) in ethyl acetate (40 ml) were added triethylamine (3.0 ml) and methanesulfonyl chloride (1.2 ml), and the mixture was stirred at room temperature for 2 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give an orange oil. To a solution of the obtained oil in N,N-dimethylformamide (30 ml) was added potassium phthalimide (1.02 g), and the mixture was stirred at 80°C for 2 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained solid was washed with diisopropyl ether and hexane to give a brown solid. To a solution of the obtained solid in methanol (100 ml) was added hydrazine monohydrate (2.19 g), and the mixture was stirred at 50°C for 1

hr. The reaction mixture was concentrated, the residue was washed with diethyl ether, and the filtrate was concentrated. The obtained residue was dissolved in ethyl acetate, and the organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propene-1-amine (1.30 g, yield: 63%) as a brown oil.

To a solution of the obtained oil (480 mg) in ethyl acetate (10 ml) were added pyridine (0.50 ml) and 1-pentanesulfonyl chloride (240 mg), and the mixture was stirred at room temperature for 30 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave N-{(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propen-1-yl}pentane-1-sulfonamide (46 mg, yield: 7%) as white crystals. melting point 106.0-106.5°C.

Example 28

To a solution of triphosgene (68 mg) in dichloromethane (5 ml) were added 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (205 mg) and pyridine (0.10 ml) under ice-cooling, and the reaction mixture was immediately concentrated. To a solution of the obtained residue in tetrahydrofuran (10 ml) were added pentane-1-sulfonamide (125 mg), N,N-diisopropylethylamine (0.40 ml) and 4-dimethylaminopyridine (62 mg), and the mixture was stirred at room temperature for 10 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated

aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (pentylsulfonyl)carbamate (35 mg, yield: 12%) as a white powder. melting point 97.5-99.0°C. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (3 H, t, J = 7.2 Hz), 1.21 - 1.52 (4 H, m), 1.71 - 1.90 (2 H, m), 1.89 - 2.05 (2 H, m), 2.58 (2 H, t, J = 7.3 Hz), 3.29 - 3.42 (2 H, m), 3.43 (3 H, s), 3.69 - 3.75 (2 H, m), 4.04 - 4.12 (2 H, m), 4.16 (2 H, t, J = 6.3 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.7, 2.4 Hz), 7.19 (1 H, d, J = 8.5 Hz), 7.34 (1 H, s), 8.02 (1 H, d, J = 2.1 Hz), 8.28 (1 H, d, J = 1.1 Hz).

Example 29

tert-Butyl {3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}[(2-nitrophenyl)sulfonyl]carbamate (3.44 g) was dissolved in a 4N hydrochloric acid ethyl acetate solution (40 ml), and the mixture was stirred at room temperature for 3 hr and at 40°C for 1 hr. After cooling to room temperature, concentrated hydrochloric acid (2.0 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. Trifluoroacetic acid (4.0 ml) was added, and the mixture was further stirred for 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:7, v/v) to give N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-2-nitrobenzenesulfonamide (2.77

g, yield: 95%) as a white solid. Recrystallization from ethyl acetate-hexane gave white feather crystals.. melting point 125.5-126.0°C.

Example 30

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (400 mg) in acetonitrile (10 ml) were added N,N-diisopropylethylamine (0.40 ml) and p-toluenesulfonylisocyanate (202 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a colorless oil. The obtained oil was dissolved in ethyl acetate, acetic anhydride (0.5 ml) and pyridine (0.5 ml) were added, and the mixture was stirred at room temperature for 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give a colorless oil. The obtained oil was subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(4-methylphenyl)sulfonyl]carbamate monohydrate (105 mg, yield:

18%) as white crystals. melting point 118-120°C.

Example 31

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (402 mg) in acetonitrile (5 ml) were added N,N-diisopropylethylamine (0.40 ml) and benzenesulfonylisocyanate (190 mg), and the mixture was stirred at room temperature for 1 hr. Acetic anhydride (0.5 ml) and pyridine (0.5 ml) were added, and the mixture was stirred at room temperature for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (phenylsulfonyl)carbamate (264.8 mg, yield: 45%) as a colorless oil. The oil was subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave white crystals as 1.5 hydrate. melting point 174-177°C.

Example 32

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (397 mg) in acetonitrile (5 ml) were added N,N-diisopropylethylamine (0.40 ml) and 4-chlorobenzenesulfonylisocyanate (218 mg), and the mixture was stirred at room temperature for 2 hr. Acetic anhydride (0.5 ml) and pyridine (0.5 ml) were added, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction

mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a colorless solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(4-chlorophenyl)sulfonyl]carbamate (161 mg, yield: 26%) as white crystals. melting point 147-150°C.

Example 33

To a solution of triphosgene (130 mg) in toluene (10 ml) were added 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (399.8 mg) and pyridine (0.10 ml) under ice-cooling, and the mixture was stirred for 5 min. 2-Chlorobenzenesulfonamide (208 mg), N,N-diisopropylethylamine (0.40 ml), 4-dimethylaminopyridine (148 mg) and tetrahydrofuran (30 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:9 - 1:1, v/v), and then subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(2-chlorophenyl)sulfonyl]carbamate (216 mg, yield: 35%) as a colorless amorphous form.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.61 - 1.75 (2 H, m), 2.30 (2 H, t, J

= 7.0 Hz), 3.41 (3 H, s), 3.62 - 3.73 (2 H, m), 3.76 - 3.86 (2 H, m), 3.97 - 4.07 (2 H, m), 6.60 (1 H, d, J = 2.4 Hz), 6.68 (1 H, dd, J = 8.4, 2.4 Hz), 7.00 (1 H, d, J = 8.5 Hz), 7.17 (1 H, s), 7.30 (2 H, s), 7.92 (1 H, d, J = 2.1 Hz), 8.07 (1 H, d, J = 7.9 Hz), 8.21 (1 H, d, J = 1.1 Hz).

Example 34

To a solution of triphosgene (136 mg) in toluene (10 ml) were added 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (396.8 mg) and pyridine (0.10 ml) under ice-cooling, and the mixture was stirred for 5 min. o-Toluenesulfonamide (181 mg), N,N-diisopropylethylamine (0.40 ml), 4-dimethylaminopyridine (142 mg) and tetrahydrofuran (30 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v), and then subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(2-methylphenyl)sulfonyl]carbamate (200 mg, yield: 34%) as a colorless amorphous form.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.59 - 1.83 (2 H, m), 2.27 - 2.41 (2 H, m), 2.56 (3 H, s), 3.41 (3 H, s), 3.60 - 3.76 (2 H, m), 3.76 - 3.91 (2 H, m), 3.98 - 4.05 (2 H, m), 6.61 (1 H, d, J = 2.4 Hz), 6.67 (1 H, d, J = 9.0 Hz), 6.96 - 7.22 (3 H, m), 7.32 (1 H, d, J = 5.5 Hz), 7.92 (1 H, d, J = 1.3 Hz), 7.97 (1 H, d, J = 7.3 Hz), 8.20 (1 H, s).

Example 35

To a solution of triphosgene (122 mg) in toluene (10 ml)

were added 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (386 mg) and pyridine (0.10 ml) under ice-cooling, and the mixture was stirred for 5 min. Butane-1-sulfonamide (142 mg), N,N-diisopropylethylamine (0.40 ml), 4-dimethylaminopyridine (122 mg) and tetrahydrofuran (30 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v), and then subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (butylsulfonyl)carbamate monohydrate (54 mg, yield: 10%) as white crystals. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 94.0-96.0°C.

Example 36

To a solution of triphosgene (142 mg) in toluene (10 ml) were added (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propen-1-ol (388 mg) and pyridine (90 μl) under ice-cooling, and the mixture was stirred for 5 min. Pentane-1-sulfonamide (194.5 mg), N,N-diisopropylethylamine (0.40 ml), 4-dimethylaminopyridine (125 mg) and tetrahydrofuran (30 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and

saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 to ethyl acetate alone, v/v), and then subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propen-1-yl (pentylsulfonyl)carbamate (14 mg, yield: 3%) as a white amorphous form.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (3 H, t, J = 7.1 Hz), 1.24 - 1.50 (4 H, m), 1.67 - 1.95 (2 H, m), 3.33 - 3.42 (2 H, m), 3.44 (3 H, s), 3.71 - 3.79 (2 H, m), 4.05 - 4.16 (2 H, m), 4.74 (2 H, dd, J = 6.7, 1.0 Hz), 5.97 - 6.31 (1 H, m), 6.55 - 6.73 (2 H, m), 6.88 (1 H, dd, J = 8.7, 2.4 Hz), 7.52 (1 H, d, J = 8.7 Hz), 8.01 (1 H, d, J = 1.9 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Example 37

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-propen-1-ol (184 mg) in acetonitrile (2.5 ml) were added N,N-diisopropylethylamine (0.40 ml) and 4-chlorobenzenesulfonylisocyanate (140 μl), and the mixture was stirred at room temperature for 30 min. 4-Chlorobenzenesulfonylisocyanate (90 μl) was further added, and the mixture was stirred for 10 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained oil was subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-

(2-methoxyethoxy)phenyl]-2-propen-1-yl [(4-chlorophenyl)sulfonyl]carbamate dihydrate (147 mg, yield: 52%) as white crystals. melting point 174.5°C (dec.).

Example 38

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (1.90 g) in toluene (25 ml) were added triethylamine (0.90 ml) and diphenylphosphorylazide (1.40 ml), and the mixture was stirred at 80°C for 1 hr. Benzyl alcohol (0.80 ml) was added, and the mixture was stirred with heating under reflux for 10 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give benzyl {2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]ethyl}carbamate (2.02 g, yield: 89%) as a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. melting point 102.5-103.0°C.

To a solution of benzyl {2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]ethyl}carbamate (450 mg) in tetrahydrofuran (5 ml) was added 10% palladium-carbon (92 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hr. The reaction mixture was filtrated and the filtrate was concentrated to give a brown oil.

The obtained oil was dissolved in ethyl acetate (5 ml), pyridine (1 ml) and 1-pentanesulfonyl chloride (227 mg) were added, and the mixture was stirred at room temperature for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium

hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v) to give N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]ethyl}pentane-1-sulfonamide (64 mg, yield: 14%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.73 - 0.94 (3 H, m), 1.15 - 1.38 (4 H, m), 1.46 - 1.77 (2 H, m), 2.59 - 2.97 (4 H, m), 3.18 - 3.33 (2 H, m), 3.43 (3 H, s), 3.60 - 3.78 (2 H, m), 3.97 - 4.14 (2 H, m), 4.55 (1 H, t, J = 5.8 Hz), 6.43 - 6.71 (1 H, m), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.08 (1 H, d, J = 8.7 Hz), 7.94 (1 H, dd, J = 8.7, 2.3 Hz), 8.43 (1 H, s).

Example 39

To a solution of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propane-1-amine (0.33 g) in acetonitrile (8 ml) was added benzenesulfonylisocyanate (0.14 ml), and the mixture was stirred overnight at room temperature. The precipitated crystals were collected by filtration, washed with acetonitrile and dried ($MgSO_4$) to give N-[({3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propyl}amino)carbonyl]benzenesulfonamide (0.29 g, yield: 57%) as colorless crystals. melting point 149°C.

Example 40

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butan-1-ol (1.00 g) in ethyl acetate (20 ml) were added triethylamine (1.20 ml) and methanesulfonyl chloride (0.70 ml), and the mixture was stirred at room temperature. After 1 hr, triethylamine (1.20 ml) and methanesulfonyl chloride (0.50 ml) were added, and the mixture was further stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and

saturated brine, dried ($MgSO_4$), filtrated and concentrated to give an orange oil.

To a solution of pentane-1-sulfonamide (679 mg) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 198 mg) under ice-cooling, and the mixture was stirred for 30 min. To the reaction mixture was added dropwise a solution of the orange oil obtained earlier in N,N-dimethylformamide (20 ml), and the mixture was stirred at 45°C for 60 hr. After cooling to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v) to give N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butyl}pentane-1-sulfonamide (238 mg, yield: 18%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.89 (3 H, t, J = 7.1 Hz), 1.19 (3 H, d, J = 7.0 Hz), 1.26 - 1.44 (4 H, m), 1.63 - 2.00 (4 H, m), 2.81 - 3.23 (5 H, m), 3.43 (3 H, s), 3.69 - 3.77 (2 H, m), 4.04 - 4.13 (2 H, m), 4.35 - 4.45 (1 H, m), 6.61 (1 H, d, J = 2.6 Hz), 6.90 (1 H, dd, J = 8.7, 2.6 Hz), 7.23 (1 H, d, J = 8.7 Hz), 8.01 (1 H, d, J = 2.3 Hz), 8.29 (1 H, d, J = 0.9 Hz).

Example 41

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylpropan-1-ol (1.22 g) in ethyl acetate (50 ml) were added triethylamine (0.80 ml) and methanesulfonyl chloride (0.35 ml), and the mixture was stirred at room temperature for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a yellow oil.

To a solution of pentane-1-sulfonamide (890 mg) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 233 mg) under ice-cooling, and the mixture was stirred for 30 min. To the reaction mixture was added dropwise a solution of the orange oil obtained earlier in N,N-dimethylformamide (10 ml), and the mixture was stirred at 50°C for 60 hr. After cooling to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 35:65, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave N-{3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylpropyl}pentane-1-sulfonamide (355 mg, yield: 22%) as white crystals. melting point 80-82°C.

Example 42

To a solution of 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}propionic acid (1.01 g) in tetrahydrofuran (30 ml) was added N,N'-carbonyldiimidazole (651 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (439 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.60 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{2-[(2,4-dichlorobenzyl)oxy]-4-isopropoxyphenyl}-N-(pentylsulfonyl)propanamide (713 mg, yield: 52%) as white crystals. melting point 120.0-120.5°C.

Example 43

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (4776 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (308 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, 3-methylbutane-1-sulfonamide (259 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), then subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(3-methylbutyl)sulfonyl]propanamide (137 mg, yield: 22%) as white crystals. melting point 130-132°C.

Example 44

To a solution of ethyl 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propionate (3.31 g) in tetrahydrofuran (15 ml) and ethanol (15 ml) was added a 1N aqueous sodium hydroxide solution (15.0 ml), and the mixture was stirred at 50°C for 1 hr. After cooling to room temperature, 1N hydrochloric acid (15.0 ml) was added, and the mixture was diluted with toluene and concentrated. The residue was dissolved in ethyl acetate. The organic layer was washed twice with saturated brine, dried ($MgSO_4$), filtrated and concentrated

to give 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propionic acid (2.91 g, yield: 93%) as a pale-yellow solid.

To a solution of 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propionic acid (2.23 g) in tetrahydrofuran (30 ml) was added N,N'-carbonyldiimidazole (1.17 g), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (1.07 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.00 ml) were added to the reaction mixture, and the mixture was stirred overnight. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 7:3, v/v) to give a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}-N-(pentylsulfonyl)propanamide (1.96 g, yield: 69%) as a white powder. melting point 111-113°C.

Example 45

To a solution of a crude product (0.67 g) of 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propionic acid in tetrahydrofuran (30 ml) was added N,N'-carbonyldiimidazole (363 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, 3-methylbutane-1-sulfonamide (343 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 ml) were added to the reaction mixture, and the mixture was stirred overnight. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried

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($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 7:3, v/v) to give a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}-N-[(3-methylbutyl)sulfonyl]propanamide (285 mg, yield: 33%) as white feather crystals. melting point 123-125°C.

Example 46

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (945 mg) in tetrahydrofuran (40 ml) was added N,N'-carbonyldiimidazole (622 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, 3-methoxypropane-1-sulfonamide (415 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.60 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v), and then subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(3-methoxypropyl)sulfonyl]propanamide (622 mg, yield: 50%) as white feather crystals. melting point 112-113°C.

Example 47

To a solution of 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-oxopyrrolidin-1-

yl)ethoxy]phenyl}propanoic acid (0.70 g) in tetrahydrofuran (15 ml) was added N,N'-carbonyldiimidazole (392 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (342 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 ml) were added to the reaction mixture, and the mixture was stirred overnight. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 to ethyl acetate alone, v/v) to give a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}-N-(pentylsulfonyl)propanamide (668 mg, yield: 74%) as a white powder. melting point 123-126°C.

Example 48

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (0.30 g) in N,N-dimethylformamide (7 ml) was added N,N'-carbonyldiimidazole (0.18 g), and the mixture was stirred at 60°C for 1.5 hr. Morpholine (193 μl) was added to the reaction mixture, and the mixture was stirred overnight. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (5:95 - 3:7, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]propyl morpholine-4-carboxylate (372 mg, yield: 98%) as a white powder. melting point 82.3-82.4°C.

Example 49

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (0.30 g) in N,N-dimethylformamide (7 ml) was added N,N'-carbonyldiimidazole (0.18 g), and the mixture was stirred at 60°C for 1 hr. 1-Butylamine (0.22 ml) was added to the reaction mixture, and the mixture was stirred for 6 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:7, v/v) to give a white solid. Recrystallization from diisopropyl ether-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl butylcarbamate (297 mg, yield: 80%) as a white powder. melting point 91.7-91.8°C.

Example 50

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (0.30 g) in N,N-dimethylformamide (7 ml) was added N,N'-carbonyldiimidazole (0.18 g), and the mixture was stirred at 60°C for 1 hr. N-Methyl-1-butylamine (0.26 ml) was added to the reaction mixture, and the mixture was stirred for 6.5 hr. N-Methyl-1-butylamine (0.26 ml) was further added, and the mixture was stirred overnight. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane

(1:9 - 3:7, v/v) to give a white solid. Recrystallization from hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl butyl(methyl)carbamate (271 mg, yield: 73%) as a white powder. melting point 54.0-55.2°C.

Example 51

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (0.30 g) in N,N-dimethylformamide (7 ml) was added N,N'-carbonyldiimidazole (0.18 g), and the mixture was stirred at 60°C for 1.5 hr. Cyclopropylmethylamine (385 μl) was added to the reaction mixture, and the mixture was stirred overnight. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:7, v/v) to give a white solid. Recrystallization from diisopropyl ether-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (cyclopropylmethyl)carbamate (272 mg, yield: 73%) as a white powder. melting point 87.8-87.9°C.

Example 52

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propyl (cyclopropylmethyl)carbamate (342 mg) in N,N-dimethylformamide (5 ml) were added potassium carbonate (225 mg) and 2-chloro-N,N-diethylacetamide (182 mg), and the mixture was stirred at 50°C for 1 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel

column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propyl (cyclopropylmethyl)carbamate (346 g, yield: 81%) as white crystals. melting point 94.0-94.5°C.

Example 53

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propyl (cyclopropylmethyl)carbamate (381 mg) in N,N-dimethylformamide (5 ml) were added potassium carbonate (252 mg) and ethyl bromoacetate (0.20 ml), and the mixture was stirred at 50°C for 30 min. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give ethyl {3-{[3-chloro-5-(trifluoromethyl)-pyridin-2-yl]oxy}-4-[3-({[(cyclopropylmethyl)amino]carbonyl}-oxy)propyl]phenoxy}acetate (383 mg, yield: 84%) as a white solid. Recrystallization from ethyl acetate-hexane gave white feather crystals. melting point 112.8-113.0°C.

Example 54

To a solution of ethyl {3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-({[(cyclopropylmethyl)amino]carbonyl}oxy)propyl]-phenoxy}acetate (301 mg) in tetrahydrofuran (5 ml) and ethanol (5 ml) was added a 1N aqueous sodium hydroxide solution (2.0 ml), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid (2.0 ml) was added to the reaction mixture, and the mixture was diluted with toluene and concentrated. The residue was dissolved in ethyl acetate. The organic layer was washed with water and saturated brine, dried

($MgSO_4$), filtrated and concentrated. The residue was recrystallized from ethyl acetate-hexane to give {3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-({[(cyclopropylmethyl)amino]carbonyl}oxy)propyl]phenoxy}acetic acid (284 mg, yield: quant.) as white feather crystals. ^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.14 - 0.21 (2 H, m), 0.42 - 0.53 (2 H, m), 0.85 - 1.05 (1 H, m), 1.74 - 1.97 (2 H, m), 2.48 - 2.58 (2 H, m), 2.96 - 3.06 (2 H, m), 4.02 (2 H, t, J = 6.3 Hz), 4.64 (2 H, s), 4.72 (1 H, s), 6.71 (1 H, d, J = 2.6 Hz), 6.82 (1 H, dd, J = 8.5, 2.4 Hz), 7.24 (1 H, d, J = 8.7 Hz), 7.99 (1 H, d, J = 2.1 Hz), 8.26 (1 H, d, J = 0.9 Hz).

Example 55

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (400 mg) in N,N-dimethylformamide (5 ml) was added N,N'-carbonyldiimidazole (222 mg), and the mixture was stirred at 40°C for 1 hr. 3-Methoxypropylamine (0.55 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (3-methoxypropyl)carbamate (276 mg, yield: 54%) as white feather crystals. melting point 83.5-85.0°C.

Example 56

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]propan-1-ol (405 mg) in N,N-dimethylformamide (5 ml) was added N,N'-carbonyldiimidazole (224 mg), and the mixture was stirred at 40°C for 1 hr. 2-Ethoxyethylamine (0.55 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (2-ethoxyethyl)carbamate (250 mg, yield: 48%) as a white powder. melting point 66-68°C.

Example 57

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]acrylic acid (598.8 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (368 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, 3-methoxypropane-1-sulfonamide (355 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.40 ml) were added to the reaction mixture, and the mixture was stirred for 3 hr. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5 - 9:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl]-N-[(3-methoxypropyl)sulfonyl]acrylamide (296 mg, yield: 37%) as a white powder. melting point 129.5-

130.0°C.

Example 58

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxyethoxy)phenyl]methanol (473 mg) in N,N-dimethylformamide (5 ml) was added N,N'-carbonyldiimidazole (295.3 mg), and the mixture was stirred at room temperature for 1 hr and at 40°C for 30 min. Then, pentane-1-sulfonamide (289 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) and 4-dimethylaminopyridine (215 mg) were added, and the mixture was subsequently stirred overnight. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:7 - 1:4, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (pentylsulfonyl)carbamate (373 mg, yield: 54%) as white crystals. melting point 130-132°C.

Example 59

To a solution of triphosgene (445 mg) in toluene (10 ml) was added a solution of 3-methylbutane-1-sulfonamide (659 mg) in toluene (5 ml) and pyridine (0.40 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. Then, [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (1.12 g), N,N-diisopropylethylamine (0.75 ml), 4-dimethylaminopyridine (574 mg) and tetrahydrofuran (15 ml) were added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium

hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(3-methylbutyl)sulfonyl]carbamate (19 mg, yield: 2%) as white feather crystals. melting point 122-124°C.

Example 60

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (501 mg) in toluene (20 ml) and tetrahydrofuran (5 ml) was added chlorosulfonylisocyanate (120 μl) with stirring under ice-cooling, and 30 min later, pyridine (0.25 ml) was added. After 1 hr, isobutylamine (0.75 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:9 - 3:2, v/v), and recrystallized from ethyl acetate-hexane to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(isobutylamino)sulfonyl]carbamate (13 mg, yield: 2%) as white crystals. melting point 160-161°C.

Example 61

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (507 mg) in toluene (20 ml) and tetrahydrofuran (5 ml) was added chlorosulfonylisocyanate (120 μl) with stirring under ice-cooling, and 30 min later, pyridine (0.25 ml) was added. After 1 hr, 1-pentylamine (0.75 ml) was added, and the mixture was stirred overnight at room

temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:2, v/v), and recrystallized from ethyl acetate-hexane to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(pentylamino)sulfonyl]carbamate (33 mg, yield: 4%) as white crystals. melting point 153-155°C.

Example 62

To a solution of (4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)methanol (1.04 g) in N,N-dimethylformamide (10 ml) was added N,N'-carbonyldiimidazole (592 mg), and the mixture was stirred at 40°C for 1 hr. Then, pentane-1-sulfonamide (584 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.60 ml) were added, and the mixture was subsequently stirred for 2 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}benzyl (pentylsulfonyl)carbamate (379 mg, yield: 25%) as a white powder. melting point 124.5-125.5°C.

Example 63

To a solution of (2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)methanol (1.00 g) in N,N-dimethylformamide (10 ml) was added N,N'-carbonyldiimidazole (621 mg), and the mixture was stirred at

40°C for 1 hr. Then, pentane-1-sulfonamide (594 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.60 ml) were added, and the mixture was subsequently stirred for 2 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxybenzyl (pentylsulfonyl)carbamate (500 mg, yield: 34%) as a white powder. melting point 70-73°C.

Example 64

To a solution of 3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(hydroxymethyl)phenyl propane-1-sulfonate (1.02 g) in N,N-dimethylformamide (10 ml) was added N,N'-carbonyldiimidazole (613 mg), and the mixture was stirred at 40°C for 1 hr. Then, pentane-1-sulfonamide (569 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.60 ml) were added, and the mixture was subsequently stirred for 2 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[({[(pentylsulfonyl)amino]carbonyl}oxy)methyl]phenyl propane-1-sulfonate (127 mg, yield: 13%) as white feather crystals. melting point 86-89°C.

Example 65

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (1.08 g) in tetrahydrofuran (15 ml) were added N,N-diisopropylethylamine (0.50 ml), 4-chlorobenzenesulfonylisocyanate (0.44 ml) and 4-dimethylaminopyridine (355 mg), and the mixture was stirred at room temperature for 30 min. 4-Chlorobenzenesulfonylisocyanate (0.44 ml) was further added, and the mixture was stirred for 1 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a colorless solid. Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(4-chlorophenyl)sulfonyl]carbamate (264 mg, yield: 16%) as a white powder. melting point 112-115°C.

Example 66

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (520 mg) in toluene (20 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added. After 1 hr, 1-butylamine (0.80 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave 2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(butylamino)sulfonyl]carbamate (542 mg, yield: 71%) as a white powder. melting point 164-165°C.

Example 67

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (521 mg) in toluene (20 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added, and after 1 hr, cyclopropylmethylamine (750 mg) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. The obtained solid was washed with diisopropyl ether, and recrystallized from ethyl acetate-diisopropyl ether to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(cyclopropylmethyl)amino]sulfonyl}carbamate (481 mg, yield: 63%) as a white powder. melting point 150.0-150.5°C.

Example 68

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (513 mg) in toluene (20 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added. After 1 hr, p-chloroaniline (659 mg) was added, and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. The obtained solid was washed with diisopropyl ether, and recrystallized

from ethyl acetate-diisopropyl ether to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(4-chlorophenyl)amino]sulfonyl}carbamate (32.1 mg, yield: 4%) as a white powder. melting point 159°C (dec.).

Example 69

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (541 mg) in toluene (20 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added. After 1 hr, morpholine (0.80 ml) was added, and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (morpholin-4-ylsulfonyl)carbamate (65 mg, 8%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.24 - 3.34 (4 H, m), 3.44 (3 H, s), 3.59 - 3.79 (6 H, m), 4.07 - 4.18 (2 H, m), 5.10 (2 H, s), 6.71 (1 H, s), 6.75 (1 H, d, J = 2.4 Hz), 6.88 (1 H, dd, J = 8.6, 2.5 Hz), 7.41 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 1.9 Hz), 8.27 (1 H, dd, J = 2.2, 1.0 Hz).

Example 70

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (506 mg) in toluene (20 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added. After 1 hr, 1-hexylamine (0.80 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric

acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) and recrystallized from ethyl acetate-diisopropyl ether to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(hexylamino)sulfonyl]carbamate (71 mg, yield: 9%) as white crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.79 - 0.97 (3 H, m), 1.17 - 1.38 (6 H, m), 1.40 - 1.55 (2 H, m), 2.94 (2 H, q, J = 7.0 Hz), 3.44 (3 H, s), 3.69 - 3.79 (2 H, m), 4.07 - 4.15 (2 H, m), 5.14 (2 H, s), 5.19 (1 H, t, J = 6.2 Hz), 6.73 (1 H, d, J = 2.4 Hz), 6.87 (1 H, dd, J = 8.5, 2.4 Hz), 7.15 (1 H, s), 7.42 (1 H, d, J = 8.5 Hz), 8.02 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Example 71

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (500 mg) in N,N-dimethylformamide (5 ml) was added N,N'-carbonyldiimidazole (337 mg), and the mixture was stirred at 40°C for 1 hr. Then, N-hexyl-N-methylsulfamide (389 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added, and the mixture was stirred at room temperature for 5 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[hexyl(methyl)amino]sulfonyl}carbamate (85 mg, yield: 11%) as

a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.76 - 0.97 (3 H, m), 1.14 - 1.36 (4 H, m), 1.41 - 1.64 (4 H, m), 2.87 (3 H, s), 3.09 - 3.23 (2 H, m), 3.44 (3 H, s), 3.67 - 3.85 (2 H, m), 4.07 - 4.18 (2 H, m), 5.08 (2 H, s), 6.74 (1 H, d, J = 2.4 Hz), 6.87 (1 H, dd, J = 8.6, 2.5 Hz), 7.04 (1 H, s), 7.41 (1 H, d, J = 8.5 Hz), 8.00 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Example 72

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (511 mg) in tetrahydrofuran (6 ml) was added N,N'-carbonyldiimidazole (314 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, N-hexyl-N-methylsulfamide (250 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred for 10 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-{[hexyl(methyl)amino]sulfonyl}propanamide (59 mg, yield: 8%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.83 - 0.93 (3 H, m), 1.19 - 1.37 (6 H, m), 1.44 - 1.57 (2 H, m), 2.52 (2 H, t, J = 7.3 Hz), 2.76 (3 H, s), 2.89 (2 H, t, J = 7.3 Hz), 3.01 - 3.12 (2 H, m), 3.42 (3 H, s), 3.68 - 3.74 (2 H, m), 3.97 - 4.11 (2 H, m), 6.56 (1 H, d, J = 2.4 Hz), 6.79 (1 H, dd, J = 8.5, 2.6 Hz), 7.19 (1 H, d, J = 8.7 Hz), 8.05 (1 H, d, J = 1.9 Hz), 8.35 (1 H, dd, J = 2.1, 0.8 Hz), 8.67 (1 H, s).

Example 73

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propionic acid (508 mg) in tetrahydrofuran (5 ml) was added N,N'-carbonyldiimidazole (296.1 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, sulfamide (221 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was recrystallized from tetrahydrofuran-diisopropyl ether to give N-(aminosulfonyl)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanamide (489 mg, yield: 81%) as a white powder. melting point 158-159°C.

Example 74

To a solution of 4-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoic acid (550.1 mg) in tetrahydrofuran (5 ml) was added N,N'-carbonyldiimidazole (321 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (261 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 4-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]-N-(pentylsulfonyl)butanamide (151 mg, yield: 21%) as white feather crystals. melting point 96-97°C.

Example 75

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (500 mg) in dichloromethane (15 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added. After 1 hr, 3-methoxypropylamine (0.80 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(3-methoxypropyl)amino]sulfonyl}carbamate (458 mg, yield: 61%) as white feather crystals. melting point 149.0-149.5°C.

Example 76

To a solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (455 mg) in dichloromethane (15 ml) was added chlorosulfonylisocyanate (0.15 ml) with stirring under ice-cooling, and 30 min later, pyridine (0.30 ml) was added. After 1 hr, 2-ethoxyethylamine (0.80 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane

(1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-ethoxyethyl)amino]sulfonyl}carbamate (301 mg, yield: 44%) as white feather crystals. melting point 142.5-143.0°C.

Example 77

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoic acid (518.8 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (309 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (218 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)butanamide (251 mg, yield: 37%) as white crystals. melting point 136.9-137.1°C.

Example 78

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]butanoic acid (511 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (290 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, 3-methoxypropane-1-sulfonamide (230 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was

dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 4:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(3-methoxypropyl)sulfonyl]butanamide (330 mg, yield: 49%) as white crystals. melting point 107-109°C.

Example 79

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (2.01 g) in tetrahydrofuran (100 ml) were added triphenylphosphine (1.81 g), tert-butyl [(2-nitrophenyl)sulfonyl]carbamate (1.81 g) and diethyl azodicarboxylate 40% toluene solution (3.80 ml) under ice-cooling, and the mixture was stirred at 0°C for 10 min and at room temperature for 1 hr. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 7:3, v/v) to give tert-butyl {3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}[(2-nitrophenyl)sulfonyl]carbamate (3.44 g, yield: quant.) as a pale-yellow solid.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.26 - 1.32 (9 H, m), 1.96 - 2.08 (2 H, m), 2.46 - 2.59 (2 H, m), 3.44 (3 H, s), 3.67 - 3.77 (4 H, m), 4:03 - 4.14 (2 H, m), 6.69 (1 H, d, J = 2.6 Hz), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 - 7.25 (1 H, m), 7.67 - 7.77 (3 H, m), 7.98 (1 H, d, J = 2.3 Hz), 8.22 - 8.30 (2 H, m).

Example 80

A mixture of 3-[1-(2,4-difluorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (140 mg), N,N'-carbonyldiimidazole (77 mg) and tetrahydrofuran (5.0 ml) was stirred with heating

under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (72 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (72 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-difluorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (50 mg, yield: 25%) as colorless crystals. melting point 107-108°C.

Example 81

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (254 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (450 mg, yield: 66%) as colorless crystals. melting point 126-129°C.

Example 82

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature,

benzenesulfonamide (264 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(phenylsulfonyl)propanamide (170 mg, yield: 24%) as colorless crystals. melting point 184-185°C.

Example 83

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 4-(trifluoromethyl)benzenesulfonamide (378 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-{[4-(trifluoromethyl)phenyl]sulfonyl}propanamide (700 mg, yield: 89%) as colorless crystals. melting point 167-169°C.

Example 84

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 1-phenylmethanesulfonamide (320 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the

concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate-hexane to give N-(benzylsulfonyl)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanamide (620 mg, yield: 87%) as colorless crystals. melting point 183-184°C.

Example 85

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, propane-1-sulfonamide (240 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(propylsulfonyl)propanamide (520 mg, yield: 80%) as colorless crystals. melting point 124-126°C.

Example 86

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (370 mg), N,N'-carbonyldiimidazole (253 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, butane-1-sulfonamide (171 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (237 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column

chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give N-(butylsulfonyl)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanamide (450 mg, yield: 66%) as colorless crystals. melting point 133-134°C.

Example 87

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, hexane-1-sulfonamide (278 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(hexylsulfonyl)propanamide (340 mg, yield: 48%) as colorless crystals. melting point 103-106°C.

Example 88

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 2-methylbenzenesulfonamide (288 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 -

3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-[(2-methylphenyl)sulfonyl]propanamide (260 mg, yield: 36%) as colorless crystals. melting point 165-166°C.

Example 89

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, propane-2-sulfonamide (207 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(isopropylsulfonyl)propanamide (350 mg, yield: 54%) as colorless crystals. melting point 135-136°C.

Example 90

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, cyclohexanesulfonamide (274 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (427 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-

hexane to give N-(cyclohexylsulfonyl)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanamide (390 mg, yield: 55%) as colorless crystals. melting point 137-138°C.

Example 91

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (341 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 3-phenylpropane-1-sulfonamide (334 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (427 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-[(3-phenylpropyl)sulfonyl]propanamide (570 mg, yield: 76%) as colorless crystals. melting point 132-134°C.

Example 92

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (400 mg), N,N'-carbonyldiimidazole (272 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 3-methylbutyl-1-sulfonamide (203 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (256 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-

hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]propanamide (400 mg, yield: 73%) as colorless crystals. melting point 143-145°C.

Example 93

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (356 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (267 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (336 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (470 mg, yield: 67%) as colorless crystals. melting point 115-117°C.

Example 94

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]acrylic acid (500 mg), N,N'-carbonyldiimidazole (343 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (256 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (322 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-

pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (220 mg, yield: 32%) as colorless crystals. melting point 109-112°C.

Example 95

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]acrylic acid (410 mg), N,N'-carbonyldiimidazole (274 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (220 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (276 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropyl-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (140 mg, yield: 24%) as colorless crystals. melting point 149-151°C.

Example 96

A mixture of 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}propanoic acid (500 mg), N,N'-carbonyldiimidazole (323 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (241 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (305 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:16 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropyl-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (260

359

mg, yield: 38%) as colorless crystals. melting point 144-145°C.

Example 97

A mixture of 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoic acid (500 mg), N,N'-carbonyldiimidazole (328 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (245 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (309 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (450 mg, yield: 66%) as colorless crystals. melting point 104-105°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 1.00 (6 H, m), 1.24 - 1.87 (10 H, m), 2.53 - 2.63 (2 H, m), 2.75 - 2.86 (2 H, m), 3.33 - 3.43 (2 H, m), 4.08 (2 H, t, J = 6.6 Hz), 5.19 (2 H, s), 5.53 (1 H, s), 6.56 (1 H, d, J = 8.5 Hz), 7.15 (1 H, dd, J = 8.5, 2.2 Hz), 7.39 (1 H, d, J = 2.2 Hz), 8.17 (1 H, brs).

Example 98

A mixture of (2E)-3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylic acid (2.50 g), N,N'-carbonyldiimidazole (1.65 g) and tetrahydrofuran (50 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (1.23 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.55 g) were added, the mixture was stirred at room temperature for 15 hr, then stirred with heating under reflux for 2 hr, and concentrated. 1N Hydrochloric acid (100 ml) was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract

was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (1.01 g, yield: 30%) as colorless crystals. melting point 95-98°C.

Example 99

To a solution of (2E)-3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acrylic acid (820 mg) in tetrahydrofuran (15 ml) were added thionyl chloride (528 mg) and N,N-dimethylformamide (20 mg) under ice-cooling, and the mixture was stirred for 1 hr. The reaction mixture was concentrated. To a solution of the residue in tetrahydrofuran (15 ml) were added 3-methylbutane-1-sulfonamide (403 mg), N,N-diisopropylethylamine (861 mg) and 4-dimethylaminopyridine (271 mg) under ice-cooling, and the mixture was stirred at room temperature for 15 hr and concentrated. 1N Hydrochloric acid (100 ml) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]acrylamide (540 mg, yield: 48%) as colorless crystals. melting point 119-120°C.

Example 100

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]propanoic acid (2.00 g), N,N'-carbonyldiimidazole (1.30 g) and tetrahydrofuran (35 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (967 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.22 g) were added. The mixture was stirred at room temperature for 15 hr, and

concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:100 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-phenyl-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (290 mg, yield: 11%) as colorless crystals. melting point 145-147°C.

Example 101

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]propanoic acid (750 mg), N,N'-carbonyldiimidazole (489 mg) and tetrahydrofuran (20 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (365 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (459 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (310 mg, yield: 30%) as colorless crystals. melting point 108-112°C.

Example 102

A mixture of 3-[3-(benzyloxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]propanoic acid (400 mg), N,N'-carbonyldiimidazole (240 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (179 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (226 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the

concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:25 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[3-(benzyloxy)-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (300 mg, yield: 56%) as colorless crystals. melting point 139-141°C.

Example 103

Under ice-cooling, to a solution of (2E)-3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (730 mg) in tetrahydrofuran (7.0 ml) were successively added thionyl chloride (471 mg) and N,N-dimethylformamide (20 mg), and the mixture was stirred for 1 hr. The reaction mixture was concentrated. The residue was dissolved in tetrahydrofuran (10 ml), and pentane-1-sulfonamide (179 mg), N,N-diisopropylethylamine (768 mg) and 4-dimethylaminopyridine (242 mg) were added under ice-cooling. The mixture was allowed to warm to room temperature, stirred for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:12 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)acrylamide (250 mg, yield: 25%) as colorless crystals. melting point 159-160°C.

Example 104

A mixture of 3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (680 mg), N,N'-carbonyldiimidazole (448 mg) and tetrahydrofuran (12 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (334 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (421 mg) were added. The

mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v) to give 3-{3-butoxy-1-[4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (170 mg, yield: 18%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (3 H, t, J = 7.1 Hz), 0.94 (3 H, t, J = 7.4 Hz), 1.23 - 1.51 (6 H, m), 1.63 - 1.80 (4 H, m), 2.50 - 2.62 (2 H, m), 2.71 - 2.83 (2 H, m), 3.27 - 3.40 (2 H, m), 4.06 (2 H, t, J = 6.6 Hz), 5.21 (2 H, s), 5.51 (1 H, s), 7.17 (2 H, d, J = 8.3 Hz), 7.55 (2 H, d, J = 8.3 Hz).

Example 105

A mixture of 3-{1-(2,4-dichlorobenzyl)-3-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]-1H-pyrazol-5-yl}propanoic acid (250 mg), N,N'-carbonyldiimidazole (148 mg) and tetrahydrofuran (5.0 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (97 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (139 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:12 - 2:1, v/v), ethyl acetate and methanol-chloroform (1:16 - 1:7, v/v), concentrated and crystallized from ethyl acetate-hexane to give 3-{1-(2,4-dichlorobenzyl)-3-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (210 mg, yield: 63%) as colorless crystals. melting point 156-158°C.

Example 106

To a solution of (2E)-3-{3-butoxy-1-[2-chloro-4-

(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (690 mg) in tetrahydrofuran (7.0 ml) were added thionyl chloride (407 mg) and N,N-dimethylformamide (20 mg) under ice-cooling, and the mixture was stirred for 1 hr. The reaction mixture was concentrated. To a solution of the residue in tetrahydrofuran (10 ml) were added pentane-1-sulfonamide (272 mg), N,N-diisopropylethylamine (663 mg) and 4-dimethylaminopyridine (209 mg) under ice-cooling, and the mixture was stirred at room temperature for 15 hr and concentrated. 1N Hydrochloric acid (100 ml) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:12 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)acrylamide (370 mg, yield: 40%) as colorless crystals. melting point 130-132°C.

Example 107

A mixture of 3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (600 mg), N,N'-carbonyldiimidazole (360 mg) and N,N-dimethylformamide (15 ml) was stirred at room temperature for 1 hr, pentane-1-sulfonamide (269 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (338 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (320 mg, yield:

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40%) as colorless crystals. melting point 131-133°C.

Example 108

A mixture of 3-[1-(2,4-dichlorobenzyl)-3-(pyridin-2-ylmethoxy)-1H-pyrazol-5-yl]propanoic acid (760 mg), N,N'-carbonyldiimidazole (455 mg) and N,N-dimethylformamide (15 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (297 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (428 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid (200 ml) and ethyl acetate (20 ml) were added to the concentrate, and the resulting precipitate was collected by filtration to give 3-[1-(2,4-dichlorobenzyl)-3-(pyridin-2-ylmethoxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide hydrochloride (500 mg, yield: 46%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.81 (3 H, t, J = 7.2 Hz), 1.14 - 1.38 (4 H, m), 1.52 - 1.67 (2 H, m), 2.57 - 2.67 (2 H, m), 2.71 - 2.83 (2 H, m), 3.27 - 3.37 (2 H, m), 5.20 (2 H, s), 5.28 (2 H, s), 5.71 (1 H, s), 6.63 (1 H, d, J = 8.4 Hz), 7.35 (1 H, dd, J = 2.1, 8.4 Hz), 7.56 - 7.74 (3 H, m), 8.08 - 8.18 (1 H, m), 8.67 (1 H, d, J = 4.8 Hz), 11.71 (1 H, m).

Example 109

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylic acid (520 mg), N,N'-carbonyldiimidazole (341 mg) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 hr, pentane-1-sulfonamide (254 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from

ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (25 mg, yield: 4%) as colorless crystals. melting point 82-85°C.

Example 110

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylic acid (520 mg), N,N'-carbonyldiimidazole (341 mg) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 hr, 3-methylbutane-1-sulfonamide (254 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]acrylamide (310 mg, yield: 44%) as colorless crystals. melting point 110-114°C.

Example 111

A mixture of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}acrylic acid (600 mg), N,N'-carbonyldiimidazole (375 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 1 hr, pentane-1-sulfonamide (279 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (352 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography,

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and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}-N-(pentylsulfonyl)acrylamide (250 mg, yield: 44%) as colorless crystals. melting point 139-140°C.

Example 112

A mixture of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}acrylic acid (600 mg), N,N'-carbonyldiimidazole (375 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 1 hr, 3-methylbutane-1-sulfonamide (279 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (352 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}-N-[(3-methylbutyl)sulfonyl]acrylamide (250 mg, yield: 44%) as colorless crystals. melting point 139-140°C.

Example 113

A mixture of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-[(3-methyloxetan-3-yl)methoxy]-1H-pyrazol-5-yl}acrylic acid (460 mg), N,N'-carbonyldiimidazole (226 mg) and N,N-dimethylformamide (15 ml) was stirred at room temperature for 1 hr, pentane-1-sulfonamide (169 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (213 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture

was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 4:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-[(3-methyloxetan-3-yl)methoxy]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)acrylamide (200 mg, yield: 38%) as colorless crystals. melting point 144-147°C.

Example 114

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]acrylic acid (1.00 g), N,N'-carbonyldiimidazole (686 mg) and N,N-dimethylformamide (25 ml) was stirred at room temperature for 1 hr, 3-methylbutane-1-sulfonamide (512 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (645 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)]-3-isopropoxy-1H-pyrazol-5-yl}-N-[(3-methylbutyl)sulfonyl]acrylamide (380 mg, yield: 28%) as colorless crystals. melting point 132-135°C.

Example 115

A mixture of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}acrylic acid (640 mg), N,N'-carbonyldiimidazole (401 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 1 hr, 3-methoxypropane-1-sulfonamide (303 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (378 mg) were added, and the mixture was stirred at 100°C for 4 hr. After cooling to room

temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}-N-[(3-methoxypropyl)sulfonyl]acrylamide (510 mg, yield: 59%) as colorless crystals. melting point 138-139°C.

Example 116

To a solution of (2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylic acid (660 mg) in tetrahydrofuran (10 ml) were added thionyl chloride (395 mg) and N,N-dimethylformamide (20 mg) under ice-cooling, and the mixture was stirred for 1 hr. The reaction mixture was concentrated. To a solution of the residue in tetrahydrofuran (10 ml) were added pentane-1-sulfonamide (301 mg), N,N-diisopropylethylamine (644 mg) and 4-dimethylaminopyridine (203 mg) under ice-cooling, and the mixture was stirred at room temperature for 15 hr and concentrated. 1N Hydrochloric acid (100 ml) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (160 mg, yield: 18%) as pale-yellow crystals. melting point 154-157°C.

Example 117

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylic acid

(660 mg), N,N'-carbonyldiimidazole (404 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 1 hr, 3-methylbutane-1-sulfonamide (301 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (380 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]acrylamide (320 mg, yield: 36%) as colorless crystals. melting point 143-144°C.

Example 118

A mixture of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}acrylic acid (660 mg), N,N'-carbonyldiimidazole (426 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 1 hr, 3-methylbutane-1-sulfonamide (318 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (401 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}-N-[(3-methylbutyl)sulfonyl]acrylamide (480 mg, yield: 54%) as colorless crystals. melting point 145-147°C.

Example 119

A mixture of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylic acid (300 mg), N,N'-carbonyldiimidazole (182 mg) and N,N-dimethylformamide (8.0 ml) was stirred at room temperature for 1 hr, 3-methoxypropane-1-sulfonamide (138 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (171 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]-N-[(3-methoxypropyl)sulfonyl]acrylamide (260 mg, yield: 65%) as colorless crystals. melting point 137-138°C.

Example 120

A mixture of 3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]propanoic acid (430 mg), N,N'-carbonyldiimidazole (260 mg) and tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 3-methoxypropane-1-sulfonamide (197 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (244 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]-N-[(3-

methoxypropyl)sulfonyl]propanamide (390 mg, yield: 68%) as colorless crystals. melting point 152-154°C.

Example 121

A mixture of (2E)-3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (840 mg), N,N'-carbonyldiimidazole (528 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 1 hr, pentane-1-sulfonamide (345 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (497 mg) were added, and the mixture was stirred at 100°C for 15 hr. After cooling to room temperature, the reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)acrylamide (400 mg, yield: 35%) as colorless crystals. melting point 147-148°C.

Example 122

A mixture of 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (700 mg), N,N'-carbonyldiimidazole (408 mg) and tetrahydrofuran (15 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (286 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (412 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:1, v/v), concentrated, and crystallized from ethyl acetate-

hexane to give 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (500 mg, yield: 53%) as colorless crystals. melting point 136-137°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (3 H, t, J = 7.1 Hz), 1.23 - 1.47 (13 H, m), 1.70 - 1.85 (2 H, m), 2.57 - 2.68 (2 H, m), 2.77 - 2.87 (2 H, m), 3.34 - 3.43 (2 H, m), 5.39 (2 H, s), 5.99 (1 H, s), 6.50 (1 H, d, J = 8.1 Hz), 7.42 (1 H, d, J = 8.1 Hz), 7.65 (1 H, s), 8.00 (1 H, brs).

Example 123

A mixture of 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}propanoic acid (500 mg), N,N'-carbonyldiimidazole (313 mg) and tetrahydrofuran (15 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 3-methoxypropane-1-sulfonamide (237 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (296 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 7:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-[(3-methoxypropyl)sulfonyl]propanamide (370 mg, yield: 55%) as colorless crystals. melting point 149-150°C.

Example 124

Under ice-cooling, to a solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (1.89 g) in N,N-dimethylformamide (20 ml) was added sodium hydride (60% in oil, 479 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was immersed in an ice bath, 1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazole-5-carbaldehyde (1.00 g) was added, and the mixture was stirred for 1 hr. The

reaction mixture was poured into saturated brine, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give tert-butyl ({(E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]vinyl}sulfonyl)carbamate (610 mg, yield: 39%) as colorless crystals. melting point 152-153°C.

Example 125

A mixture of hexanoic acid (107 mg), N,N'-carbonyldiimidazole (299 mg) and tetrahydrofuran (6 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, (E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethylenesulfonamide (300 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (305 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give N-({(E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]vinyl}sulfonyl)hexanamide (110 mg, yield: 29%) as colorless crystals. melting point 73-75°C.

Example 126

A mixture of hexanoic acid (98 mg), N,N'-carbonyldiimidazole (273 mg) and tetrahydrofuran (4 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, 2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethanesulfonamide (220 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (256 mg) were added. The mixture was stirred at room temperature for 15 hr, and concentrated. 1N Hydrochloric acid was added to the

concentrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give N-({2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethyl}sulfonyl)hexanamide (25 mg, yield: 9%) as colorless crystals. melting point 107-108°C.

Example 127

Under ice-cooling, to a solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (7.24 g) in N,N-dimethylformamide (120 ml) was added sodium hydride (60% in oil, 479 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled with an ice bath, 3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazole-5-carbaldehyde (4.00 g) was added, and the mixture was stirred for 1 hr. The reaction mixture was poured into saturated brine, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give tert-butyl ({(E)-2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]vinyl}sulfonyl)carbamate (610 mg, yield: 39%) as colorless crystals. melting point 152-153°C.

Example 128

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (500 mg), 4-pyrrolidinopyridine (182 mg) and pyridine (10 ml) was added hexanoyl chloride (497 mg), and the mixture was stirred at room temperature for 20 hr. The reaction mixture was poured into 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogencarbonate solution,

saturated brine, dried ($MgSO_4$), and concentrated. To a mixture of the residue, 4-dimethylaminopyridine (299 mg), N,N-diisopropylethylamine (318 mg), and N,N-dimethylacetamide (10 ml) was added hexanoyl chloride (331 mg) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give N-({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)hexanamide (250 mg, yield: 40%) as colorless crystals. melting point 90-92°C.

Example 129

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (500 mg), 4-dimethylaminopyridine (299 mg), N,N-diisopropylethylamine (318 mg) and N,N-dimethylacetamide (10 ml) was added butyl chloroformate (336 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give butyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (420 mg, yield: 67%) as colorless crystals. melting point 108-111°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (3 H, t, J = 7.2 Hz), 0.95 (3 H, t, J = 7.2 Hz), 1.30 - 1.80 (8 H, m), 2.97 - 3.07 (2 H, m), 3.58 - 3.68 (2 H, m), 4.08 (2 H, t, J = 6.6 Hz), 4.17 (2 H, t, J = 6.6 Hz), 5.18 (2 H, s), 5.60 (1 H, s), 6.61 (1 H, d, J = 8.3 Hz), 7.16 (1 H, dd, J = 8.3, 2.1 Hz), 7.39 (1 H, d, J =

2.1 Hz).

Example 130

Under ice-cooling, to a mixture of (E)-2-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]ethylenesulfonamide (1.00 g), 4-dimethylaminopyridine (604 mg), N,N-diisopropylethylamine (640 mg) and N,N-dimethylacetamide (20 ml) was added butyl chloroformate (676 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:24 - 1:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give butyl ({(E)-2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]vinyl}sulfonyl)carbamate (470 mg, yield: 38%) as colorless crystals. melting point 137-138°C.

Example 131

Under ice-cooling, to a mixture of (E)-2-[1-(2,4-dichlorobenzyl)-3-butoxy-1H-pyrazol-5-yl]ethylenesulfonamide (1.00 g), 4-dimethylaminopyridine (604 mg), N,N-diisopropylethylamine (640 mg) and N,N-dimethylacetamide (20 ml) was added hexanoyl chloride (666 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give N-({(E)-2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]vinyl}sulfonyl)hexanamide (830 mg, yield: 67%) as colorless crystals. melting point 117-119°C.

Example 132

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added propyl chloroformate (181 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give propyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (250 mg, yield: 69%) as colorless crystals. melting point 92-94°C.

Example 133

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added isobutyl chloroformate (202 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give isobutyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (280 mg, yield: 75%) as colorless crystals. melting point 114-116°C.

Example 134

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-

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dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added 2-methoxyethyl chloroformate (205 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 2-metoxyethyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (280 mg, yield: 75%) as colorless crystals. melting point 82-86°C.

Example 135

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added pentyl chloroformate (223 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give pentyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (250 mg, yield: 65%) as colorless crystals. melting point 91-93°C.

Example 136

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added benzyl chloroformate (252 mg), and the mixture was stirred at room

temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:19 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give benzyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (130 mg, yield: 33%) as colorless crystals. melting point 99-101°C.

Example 137

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added allyl chloroformate (178 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give allyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (200 mg, yield: 55%) as colorless crystals. melting point 94-95°C.

Example 138

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added hexyl chloroformate (178 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with

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water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give benzyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (160 mg, yield: 41%) as colorless crystals. melting point 92-95°C.

Example 139

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added isopropyl chloroformate (181 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give isopropyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (240 mg, yield: 66%) as colorless crystals. melting point 120-121°C.

Example 140

Under ice-cooling, to a mixture of 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethanesulfonamide (300 mg), 4-dimethylaminopyridine (181 mg), N,N-diisopropylethylamine (191 mg) and N,N-dimethylacetamide (5 ml) was added 2,2-dimethylpropyl chloroformate (223 mg), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-

hexane (1:24 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 2,2-dimethylpropyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate (150 mg, yield: 39%) as colorless crystals. melting point 116-118°C.

Example 141

Under ice-cooling, to a mixture of 3-methylbutane-1-sulfonamide (230 mg), pyridine (156 mg) and toluene (10 ml) was added triphosgene (226 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was immersed in an ice bath, [1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]methanol (400 mg), N,N-diisopropylethylamine (821 mg), 4-dimethylaminopyridine (155 mg) and tetrahydrofuran (10 ml) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give [1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]methyl [(3-methylbutyl)sulfonyl]carbamate (210 mg, yield: 34%) as colorless crystals. melting point 104-107°C.

Example 142

Under ice-cooling, to a mixture of pentane-1-sulfonamide (289 mg), pyridine (196 mg) and toluene (10 ml) was added triphosgene (283 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was immersed in an ice bath, [1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]methanol (500 mg), N,N-diisopropylethylamine (1.03 g), 4-dimethylaminopyridine (194 mg) and tetrahydrofuran (10 ml) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added to the residue, and the mixture

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was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give [1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]methyl (pentylsulfonyl)carbamate (150 mg, yield: 19%) as colorless crystals. melting point 126-128°C.

Example 143

To a solution of 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}propionic acid (502 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (310 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, pentane-1-sulfonamide (201 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred for 7 hr. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-isopropoxy-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (39 mg, yield: 6%) as white crystals. melting point 147.0-149.0°C.

Example 144

To a solution of ethyl 3-[3-isopropoxy-1-(pyridin-2-ylmethyl)-1H-pyrazol-5-yl]propionate (1.09 g) in tetrahydrofuran (3.5 ml) and ethanol (3.5 ml) was added a 1N aqueous sodium hydroxide solution (7.5 ml), and the mixture was stirred at 50°C for 1 hr. After cooling to room temperature, 1N hydrochloric acid (7.5 ml) was added,

concentrated, and the residue was dissolved in ethyl acetate. The organic layer was washed twice with saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid.

To a solution of the obtained solid in tetrahydrofuran (8 ml) was added N,N'-carbonyldiimidazole (167 mg), and the mixture was heated under reflux for 1.5 hr. After cooling to room temperature, pentane-1-sulfonamide (115 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 ml) were added to the reaction mixture, and the mixture was stirred for 4 hr. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 4:1, v/v) to give 3-[3-isopropoxy-1-(pyridin-2-ylmethyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide (45 mg, yield: 15%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.94 (3 H, m), 1.24 (6 H, d, J = 6.2 Hz), 1.27 - 1.45 (4 H, m), 1.64 - 1.81 (2 H, m), 2.66 (2 H, t, J = 7.1 Hz), 3.07 (2 H, t, J = 7.1 Hz), 3.16 - 3.27 (2 H, m), 4.50 - 4.65 (1 H, m), 5.16 (2 H, s), 5.48 (1 H, s), 7.30 - 7.38 (1 H, m), 7.43 (1 H, d, J = 7.7 Hz), 7.75 - 7.85 (1 H, m), 8.70 (1 H, d, J = 4.1 Hz).

Example 145

To a solution of [3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]acetic acid (501 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (322 mg), and the mixture was heated under reflux for 50 min. After cooling to room temperature, pentane-1-sulfonamide (215 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated.

The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give 2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acetamide (171 mg, yield: 25%) as a pale-orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.81 - 1.08 (6 H, m), 1.23 - 1.90 (10 H, m), 3.25 - 3.36 (2 H, m), 3.60 (2 H, s), 4.11 (2 H, t, J = 6.6 Hz), 5.20 (2 H, s), 5.74 (1 H, s), 6.75 (1 H, d, J = 8.3 Hz), 7.19 (1 H, dd, J = 8.4, 2.0 Hz), 7.39 (1 H, d, J = 2.1 Hz).

Example 146

To a solution of 4-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]butanoic acid (1.36 g) in tetrahydrofuran (15 ml) was added N,N'-carbonyldiimidazole (891 mg), and the mixture was heated under reflux for 1 hr 20 min. After cooling to room temperature, pentane-1-sulfonamide (645 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.80 ml) were added to the reaction mixture, and the mixture was stirred for 6 hr. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution, and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 4-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)butanamide (989 mg, yield: 54%) as white crystals. melting point 121.0-122.0°C.

Example 147

To a solution of 5-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]pentanoic acid (433 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (312 mg), and the mixture was heated under reflux for 30 min. After cooling to room temperature, pentane-1-sulfonamide (205 mg) and 1,8-

diazabicyclo[5.4.0]undec-7-ene (0.25 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 5-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)pentanamide (290 mg, yield: 50%) as white crystals. melting point 91-93°C.

Example 148

A solution of 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]propanoic acid (0.50 g) and N,N'-carbonyldiimidazole (0.25 g) in tetrahydrofuran (10 ml) was stirred with heating under reflux for 1 hr. After cooling to room temperature, methanesulfonamide (0.15 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.24 ml) were added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid (8 ml) and brine (10 ml) were added to the reaction mixture, and the mixture was extracted with ethyl acetate (20 ml×2). The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:1, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-[1-(2,4-dichlorobenzyl)-3-isopropoxy-1H-pyrazol-5-yl]-N-(methylsulfonyl)propanamide (0.53 g, yield: 86%) as colorless crystals. melting point 104-105°C.

Example 149

A solution of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylic acid (405 mg) and N,N'-carbonyldiimidazole (195 mg)

in N,N-dimethylformamide (4 ml) was stirred at room temperature for 1 hr. To the mixture were added pentane-1-sulfonamide (181 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.179 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture to adjust the pH to about 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 2:3, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (278 mg, yield: 52%) as colorless crystals. melting point 130.5-132.5°C.

Example 150

A solution of (2E)-3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}acrylic acid (500 mg) and N,N'-carbonyldiimidazole (250 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To the mixture were added 3-methylbutane-1-sulfonamide (233 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.232 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 2:3, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-{3-butoxy-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-[(3-methylbutyl)sulfonyl]acrylamide (304 mg, yield: 57%) as

colorless crystals. melting point 89.5-90.5°C.

Example 151

A solution of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]acrylic acid (500 mg) and N,N'-carbonyldiimidazole (250 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To the mixture were added pentane-1-sulfonamide (233 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.232 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 2:3, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(cyclopropylmethoxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (345 mg, yield: 65%) as colorless crystals. melting point 148-151°C.

Example 152

A solution of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]acrylic acid (500 mg) and N,N'-carbonyldiimidazole (240 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To the mixture were added 3-methylbutane-1-sulfonamide (224 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.222 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to

silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 2:3, v/v), and concentrated. The obtained crude crystals were recrystallized from ethyl acetate-hexane. Diisopropyl ether was added to the obtained crude crystals, and the mixture was stirred for 1 hr, and recrystallized from methanol-water to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(2-methoxyethoxy)-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]acrylamide (292 mg, yield: 54%) as colorless crystals. melting point 114-116°C.

Example 153

A solution of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylic acid (535 mg) and N,N'-carbonyldiimidazole (221 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To the mixture were added 3-methylbutane-1-sulfonamide (206 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.203 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:10 - 1:2, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]-N-[(3-methylbutyl)sulfonyl]acrylamide (315 mg, yield: 45%) as colorless crystals. melting point 149.5-152.5°C.

Example 154

A solution of (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]acrylic acid (535 mg) and N,N'-carbonyldiimidazole (221 mg) in N,N-dimethylformamide (5 ml)

was stirred at room temperature for 1 hr. To the mixture were added pentane-1-sulfonamide (206 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.203 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:10 - 1:2, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[1-[2-chloro-4-(trifluoromethyl)benzyl]-3-(tetrahydro-2H-pyran-4-yloxy)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)acrylamide (337 mg, yield: 48%) as colorless crystals. melting point 160.5-161°C.

Example 155

A solution of (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}acrylic acid (501 mg) and N,N'-carbonyldiimidazole (242 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To the mixture were added pentane-1-sulfonamide (225 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.223 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:20 - 1:2, v/v), concentrated, and the obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}-N-(pentylsulfonyl)acrylamide (313 mg, yield: 46%) as colorless

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crystals. melting point 139-140.5°C.

Example 156

A solution of 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}propanoic acid (450 mg) and N,N'-carbonyldiimidazole (216 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. To the mixture were added pentane-1-sulfonamide (201 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.199 ml), and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:20 - 1:2, v/v), and concentrated. The obtained crude crystals were recrystallized from ethyl acetate-hexane. The obtained crude crystals were purified by HPLC (acetonitrile:water, containing 0.01% TFA, 40:60 - 100:0, v/v), and recrystallized from ethyl acetate-hexane to give 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide (261 mg, yield: 43%) as colorless crystals. melting point 151.5-153.5°C.

Example 157

A solution of 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}propanoic acid (450 mg) and N,N'-carbonyldiimidazole (216 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 1 hr. 3-Methylbutane-1-sulfonamide (201 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.199 ml) were added, and the mixture was stirred at 100°C for 12 hr. After cooling to room temperature, 1N hydrochloric acid was added to the reaction mixture, and the mixture was adjusted to about pH 4. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated

and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:20 - 1:2, v/v), and concentrated. The obtained crude crystals were recrystallized from ethyl acetate-hexane. The obtained crude crystals were purified by HPLC (acetonitrile:water, containing 0.01% TFA, 40:60 - 100:0, v/v), and recrystallized from ethyl acetate-hexane to give 3-{1-[2-chloro-4-(trifluoromethyl)benzyl]-3-cyclopropyl-1H-pyrazol-5-yl}-N-[(3-methylbutyl)sulfonyl]propanamide (191 mg, yield: 31%) as colorless crystals. melting point 160.5-162.5°C.

Example 158

To a solution (10 ml) of (2E)-3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (0.86 g) in acetonitrile, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.74 g), 4-dimethylaminopyridine (0.47 g) and pentane-1-sulfonamide (0.43 g) were added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, water was poured into the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (0.30 g, yield: 25%) as colorless crystals. melting point 97.5-98.3°C.

Example 159

A solution of (2E)-3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (165 mg) and 10% palladium-carbon (40 mg) in methanol (20 ml) was stirred under a hydrogen atmosphere at room temperature for 2 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane

(3:7, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-[2-(cyclohexylmethoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide (151 mg, yield: 91%) as colorless crystals. melting point 81.0-82.0°C.

Example 160

To a solution of (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (400 mg) in tetrahydrofuran (8 ml) was added N,N'-carbonyldiimidazole (338 mg), and the mixture was heated under reflux for 30 min. After cooling to room temperature, 1,8-diazabicyclo[5.4.0]-7-undecene (310 mg) and pentane-1-sulfonamide (215 mg) were added to the reaction mixture, and the mixture was stirred at 60°C for 100 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (147 mg, yield: 25%) as colorless crystals. melting point 64.8-66.3°C.

Example 161

To a mixed solution of (2E)-3-[2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (558 mg) in acetonitrile (8 ml) and N,N-dimethylformamide (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (334 mg), 4-dimethylaminopyridine (246 mg) and pentane-1-sulfonamide (232 mg), and the mixture was stirred at room temperature for 5 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:2, v/v) to give tert-butyl 4-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-

3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)piperidine-1-carboxylate (177 mg, yield: 24%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.2 Hz), 1.25 - 1.47 (4 H, m), 1.47 (9 H, s), 1.83 - 1.86 (4 H, m), 1.92 - 2.00 (2 H, m), 3.26 - 3.32 (2 H, m), 3.45 (3 H, s), 3.46 - 3.54 (2 H, m), 3.74 - 3.79 (4 H, m), 4.13 - 4.16 (2 H, m), 4.47 - 4.53 (1 H, m), 6.43 (1 H, d, J = 15.6 Hz), 6.51 - 6.52 (2 H, m), 7.41 - 7.44 (1 H, m), 7.95 (1 H, d, J = 15.6 Hz), 8.12 (1 H, brs).

Example 162

A solution of tert-butyl 4-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)piperidine-1-carboxylate (181 mg) and 10% palladium-carbon (40 mg) in methanol (20 ml) was stirred under a hydrogen atmosphere at room temperature for 2 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give tert-butyl 4-(5-(2-methoxyethoxy)-2-{3-oxo-3-[(pentylsulfonyl)amino]propyl}phenoxy)piperidine-1-carboxylate (147 mg) as a colorless amorphous solid. To a solution of the obtained colorless amorphous solid in ethyl acetate (4 ml) was added a 4N hydrogen chloride ethyl acetate solution (2 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated and dried to give (2E)-3-[4-(2-methoxyethoxy)-2-(piperidin-4-yloxy)phenyl]-N-(pentylsulfonyl)acrylamide (123 mg, yield: 94%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.84 (3 H, t, J = 7.1 Hz), 1.23 - 1.31 (4 H, m), 1.50 - 1.60 (2 H, m), 1.79 - 1.90 (2 H, m), 2.02 - 2.13 (2 H, m), 2.48 - 2.50 (2 H, m), 2.70 - 2.75 (2 H, m), 3.10 - 3.18 (4 H, m), 3.27 - 3.29 (2 H, m), 3.29 (3 H, s), 3.62 - 3.64 (2 H, m), 4.02 - 4.05 (2 H, m), 4.65 - 4.70 (1 H, m), 6.45 (1 H, d, J = 8.2 Hz), 6.61 (1 H, s), 7.02 (1 H, d, J

= 8.2 Hz), 8.73 (2 H, brs), 11.61 (1 H, brs).

Example 163

To a solution of (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (517 mg) in tetrahydrofuran (10 ml) was added N,N'-carbonyldiimidazole (392 mg), and the mixture was heated under reflux for 1 hr. After cooling to room temperature, 1,8-diazabicyclo[5.4.0]-7-undecene (386 mg), 4-dimethylaminopyridine (238 mg) and pentane-1-sulfonamide (374 mg) were added to the reaction mixture, and the mixture was heated under reflux for 22 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (321 mg, yield: 44%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.1 Hz), 1.31 - 1.45 (6 H, m), 1.52 - 1.65 (4 H, m), 1.78 - 1.90 (4 H, m), 1.97 - 2.05 (2 H, m), 3.46 (3 H, s), 3.48 - 3.55 (2 H, m), 3.76 - 3.77 (2 H, m), 4.13 - 4.16 (2 H, m), 4.26 - 4.35 (1 H, m), 6.45 - 6.53 (3 H, m), 7.40 (1 H, d, J = 8.4 Hz), 7.70 (1 H, brs), 7.94 (1 H, d, J = 15.6 Hz).

Example 164

A solution of (2E)-3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (238 mg) and 10% palladium-carbon (40 mg) in methanol (20 ml) was stirred under a hydrogen atmosphere at room temperature for 3 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7, v/v) to give 3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide (246 mg, yield: 99%) as colorless crystals. melting point 64.1-65.4°C.

Example 165

To a solution of (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylic acid (500 mg) in acetonitrile (5 ml) were added 2-methyl-6-nitrobenzoic anhydride (533 mg), triethylamine (495 mg), 4-dimethylaminopyridine (189 mg) and pentane-1-sulfonamide (239 mg), and the mixture was stirred at room temperature for 28 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (489 mg, yield: 69%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.1 Hz), 1.26 - 1.48 (4 H, m), 1.71 - 2.20 (6 H, m), 3.45 (3 H, s), 3.45 - 3.54 (2 H, m), 3.74 - 3.77 (2 H, m), 3.85 - 4.02 (4 H, m), 4.11 - 4.16 (2 H, m), 4.35 - 4.42 (1 H, m), 6.52 - 6.54 (2 H, m), 6.61 (1 H, d, J = 15.6 Hz), 7.38 (1 H, d, J = 8.1 Hz), 7.85 (1 H, d, J = 15.6 Hz), 8.56 (1 H, brs).

Example 166

A solution of (2E)-3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (319 mg) and 10% palladium-carbon (40 mg) in methanol (20 ml) was stirred under a hydrogen atmosphere at room temperature for 2 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]-N-(pentylsulfonyl)propanamide (296 mg, yield: 92%) as colorless crystals. melting point 57.8-58.9°C.

Example 167

A solution of (2E)-3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (268 mg) and 10% palladium-carbon (41 mg) in methanol (20 ml) was stirred under a hydrogen atmosphere at room temperature for 2 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide (230 mg, yield: 85%) as colorless crystals. melting point 81.7-82.8°C.

Example 168

To a solution of (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (530 mg) in acetonitrile (10 ml) were added 2-methyl-6-nitrobenzoic anhydride (461 mg), triethylamine (410 mg), 4-dimethylaminopyridine (166 mg) and pentane-1-sulfonamide (203 mg), and the mixture was stirred at room temperature for 40 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (385 mg, yield: 54%) as colorless crystals. melting point 137.6-138.2°C.

Example 169

To a mixed solution of (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (210 mg) in methanol (15 ml) and tetrahydrofuran (15 ml) was added a palladium-activated carbon

ethylenediamine complex (30 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide (128 mg, yield: 60%) as colorless crystals. melting point 106.7-108.2°C.

Example 170

To a solution of (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (600 mg) in N,N-dimethylformamide (6 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (407 mg), 4-dimethylaminopyridine (290 mg) and pentane-1-sulfonamide (241 mg), and the mixture was stirred at room temperature for 72 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (352 mg, yield: 43%) as colorless crystals. melting point 119.0-120.3°C.

Example 171

To a mixed solution of (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (167 mg) in methanol (10 ml) and tetrahydrofuran (10 ml) was added palladium-activated carbon ethylenediamine complex (20 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 7 hr. The catalyst was filtered off, and the filtrate was concentrated.

The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide (116 mg, yield: 69%) as colorless crystals. melting point 92.2-93.6°C.

Example 172

To a solution of (2E)-3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}acrylic acid (650 mg) in acetonitrile (10 ml) were added 2-methyl-6-nitrobenzoic anhydride (543 mg), triethylamine (489 mg), 4-dimethylaminopyridine (195 mg) and pentane-1-sulfonamide (242 mg), and the mixture was stirred at room temperature for 24 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give (2E)-3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}-N-(pentylsulfonyl)acrylamide (780 mg, yield: 91%) as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.87 (3 H, t, J = 7.1 Hz), 1.27 - 1.40 (4 H, m), 1.75 - 1.83 (2 H, m), 2.43 (3 H, s), 3.40 - 3.44 (2 H, m), 3.45 (3 H, s), 3.74 - 3.78 (2 H, m), 4.16 - 4.19 (2 H, m), 5.03 (2 H, s), 6.53 - 6.58 (2 H, m), 6.76 (1 H, d, J = 2.1 Hz), 7.38 - 7.48 (4 H, m), 7.85 - 7.91 (2 H, m), 7.99 - 8.02 (2 H, m).

Example 173

A solution of (2E)-3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}-N-(pentylsulfonyl)acrylamide (270 mg) and 10% palladium-carbon (40 mg) in methanol (30 ml) was stirred under a hydrogen atmosphere at room temperature for 4 hr. The catalyst was

filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 3-{4-(2-methoxyethoxy)-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}-N-(pentylsulfonyl)propanamide (240 mg, yield: 88%) as colorless crystals. melting point 95.9-96.7°C.

Example 174

To a solution of (2E)-3-{4-(2-methoxyethoxy)-2-[2-nitro-5-(trifluoromethyl)phenoxy]phenyl}acrylic acid (443 mg) in acetonitrile (8 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (309 mg), 4-dimethylaminopyridine (164 mg) and pentane-1-sulfonamide (157 mg), and the mixture was stirred at room temperature for 14 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-{4-(2-methoxyethoxy)-2-[2-nitro-5-(trifluoromethyl)phenoxy]phenyl}-N-(pentylsulfonyl)acrylamide (75 mg, yield: 13%) as colorless crystals. melting point 164.5-165.2°C.

Example 175

To a solution of (2E)-3-[2-[2-chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (715 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (502 mg), 4-dimethylaminopyridine (278 mg) and pentane-1-sulfonamide (261 mg), and the mixture was stirred at room temperature for 18 hr. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and

concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[2-chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (285 mg, yield: 30%) as colorless crystals. melting point 134.1-135.1°C.

Example 176

To a solution of (2E)-3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)acrylic acid (350 mg) in acetonitrile (6 ml) were added 2-methyl-6-nitrobenzoic anhydride (350 mg), triethylamine (283 mg), 4-dimethylaminopyridine (135 mg) and pentane-1-sulfonamide (144 mg), and the mixture was stirred at room temperature for 30 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)-N-(pentylsulfonyl)acrylamide (149 mg, yield: 31%) as yellow crystals. melting point 142.3-142.6°C.

Example 177

A solution of (2E)-3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)-N-(pentylsulfonyl)acrylamide (200 mg) and 10% palladium-carbon (35 mg) in methanol (20 ml) was stirred under a hydrogen atmosphere at room temperature for 2 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v) to give 3-(4-(2-methoxyethoxy)-2-{[4-(trifluoromethyl)phenyl]amino}phenyl)-N-

(pentylsulfonyl)propanamide (101 mg, yield: 50%) as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.86 (3 H, t, J = 6.9 Hz), 1.22 - 1.38 (4 H, m), 1.62 - 1.71 (2 H, m), 2.65 (2 H, t, J = 6.5 Hz), 2.88 (2 H, t, J = 6.5 Hz), 3.29 - 3.34 (2 H, m), 3.43 (3 H, s), 3.71 - 3.73 (2 H, m), 4.03 - 4.06 (2 H, m), 6.58 (1 H, s), 6.70 (1 H, dd, J = 8.4, 2.4 Hz), 6.86 (1 H, d, J = 2.4 Hz), 6.92 (2 H, d, J = 8.7 Hz), 7.11 (1 H, d, J = 8.4 Hz), 7.45 (2 H, d, J = 8.7 Hz), 7.84 (1 H, s).

Example 178

To a solution of (2E)-3-[2-[(5-bromo-1,3-thiazol-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (660 mg) in acetonitrile (10 ml) were added 2-methyl-6-nitrobenzoic anhydride (573 mg), triethylamine (497 mg), 4-dimethylaminopyridine (206 mg) and pentane-1-sulfonamide (249 mg), and the mixture was stirred at room temperature for 20 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(5-bromo-1,3-thiazol-2-yl)methyl]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (676 mg, yield: 77%) as yellow crystals. melting point 88.5-89.1°C.

Example 179

To a solution of tert-butyl 4-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)piperidine-1-carboxylate (1.02 g) in ethyl acetate (12 ml), a 4N hydrogen chloride ethyl acetate solution (6 ml) was added, and the mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated and dried to give (2E)-3-[4-(2-methoxyethoxy)-2-(piperidin-4-yloxy)phenyl]-N-(pentylsulfonyl)acrylamide hydrochloride (859 mg, yield:

95%) as a pale-yellow amorphous solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.85 (3 H, t, J = 7.1 Hz), 1.22 - 1.40 (4 H, m), 1.60 - 1.72 (2 H, m), 1.80 - 1.95 (2 H, m), 2.10 - 2.18 (2 H, m), 3.02 - 3.30 (4 H, m), 3.30 (3 H, s), 3.34 - 3.48 (2 H, m), 3.64 - 3.66 (2 H, m), 4.14 - 4.17 (2 H, m), 4.77 - 4.82 (1 H, m), 6.57 (1 H, d, J = 15.6 Hz), 6.66 (1 H, d, J = 8.7 Hz), 6.75 (1 H, s), 7.49 (1 H, d, J = 8.7 Hz), 7.79 (1 H, d, J = 15.6 Hz), 8.62 (1 H, brs), 8.83 (1 H, brs), 11.76 (1 H, s).

Example 180

To a solution of (2E)-3-[4-(2-methoxyethoxy)-2-(piperidin-4-yloxy)phenyl]-N-(pentylsulfonyl)acrylamide hydrochloride (175 mg) in pyridine (5 ml) were added acetic anhydride (110 mg) and 4-dimethylaminopyridine (45 mg), and the mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated, a saturated aqueous ammonium chloride solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-methanol (19:1, v/v) to give (2E)-3-[2-[(1-acetylpiperidin-4-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (110 mg, yield: 62%) as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.1 Hz), 1.25 - 1.45 (4 H, m), 1.80 - 2.06 (6 H, m), 2.13 (3 H, s), 3.39 - 3.55 (7 H, m), 3.70 - 3.74 (1 H, m), 3.74 - 3.77 (2 H, m), 3.85 - 3.95 (1 H, m), 4.13 - 4.16 (2 H, m), 4.59 - 4.63 (1 H, m), 6.51 - 6.56 (3 H, m), 7.42 (1 H, d, J = 9.3 Hz), 7.91 (1 H, d, J = 15.6 Hz), 8.90 (1 H, brs).

Example 181

To a solution of (2E)-3-[4-(2-methoxyethoxy)-2-(piperidin-4-yloxy)phenyl]-N-(pentylsulfonyl)acrylamide hydrochloride (190 mg) in pyridine (5 ml) were added benzoyl

chloride (91 mg) and triethylamine (83 mg), and the mixture was stirred at room temperature for 20 hr. The reaction mixture was concentrated, a saturated aqueous ammonium chloride solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (4:1, v/v) to give (2E)-3-[2-[(1-benzoylpiperidin-4-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (163 mg, yield: 75%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.89 (3 H, t, J = 7.1 Hz), 1.25 - 1.46 (4 H, m), 1.78 - 2.20 (6 H, m), 3.30 - 3.55 (6 H, m), 3.55 - 3.90 (4 H, m), 3.93 - 4.18 (3 H, m), 4.61 - 4.65 (1 H, m), 6.45 - 6.53 (3 H, m), 7.38 - 7.43 (6 H, m), 7.96 (1 H, d, J = 15.9 Hz), 8.54 (1 H, s).

Example 182

To a solution of (2E)-3-[2-[(5-bromo-1,3-thiazol-2-yl)methyl]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (260 mg) in 1,2-dimethoxyethane (6 ml) were added dihydroxyphenylborane (84 mg), a 2N sodium carbonate aqueous solution (0.5 ml) and tetrakis(triphenylphosphine)palladium (0) (56 mg), and the mixture was heated under reflux for 7 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v) to give (2E)-3-{4-(2-methoxyethoxy)-2-[(5-phenyl-1,3-thiazol-2-yl)methyl]phenyl}-N-(pentylsulfonyl)acrylamide (135 mg, yield: 52%) as a pale-yellow amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.87 (3 H, t, J = 7.1 Hz), 1.25 - 1.39 (4 H, m), 1.78 - 1.88 (2 H, m), 3.43 (3 H, s), 3.43 - 3.49 (2 H, m), 3.73 - 3.76 (2 H, m), 4.13 - 4.16 (2 H, m),

6.49 (1 H, d, J = 15.9 Hz), 6.86 - 6.92 (2 H, m), 7.31 - 7.44 (6 H, m), 7.51 (1 H, d, J = 9.0 Hz), 7.86 (1 H, d, J = 15.9 Hz), 8.59 (1 H, s).

Example 183

To a solution of 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzaldehyde (1.40 g) in acetic acid (7 ml) were added ethylmalonic acid (2.46 g) and pyrrolidine (3.73 g), and the mixture was stirred at 100°C for 72 hr. 1N Hydrochloric acid (1.5 ml) and water (14 ml) were added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7, v/v) to give (2E)-2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzylidene]butanoic acid (450 mg) as a brown oil. To a solution of the obtained oil in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (276 mg), triethylamine (275 mg), 4-dimethylaminopyridine (101 mg) and pentane-1-sulfonamide (126 mg), and the mixture was stirred at room temperature for 18 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzylidene]-N-(pentylsulfonyl)butanamide (63 mg, yield: 3%) as colorless crystals. melting point 104.5-105.6°C.

Example 184

To a solution of (2E)-3-[2-{[2-chloro-4-(trifluoromethyl)phenyl]amino}-4-(2-methoxyethoxy)phenyl]acrylic acid (487 mg) in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (449 mg), triethylamine (370 mg), 4-dimethylaminopyridine (144 mg) and pentane-1-sulfonamide (177 mg), and the mixture was stirred at room temperature for 22 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-{[2-chloro-4-(trifluoromethyl)phenyl]amino}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (255 mg, yield: 39%) as yellow crystals. melting point 173.5-174.8°C.

Example 185

To a mixed solution of ethyl (2E)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-nitropyridin-2-yl)oxy]phenyl}acrylate (630 mg) in tetrahydrofuran (8 ml) and ethanol (8 ml) was added a 1N aqueous sodium hydroxide solution (3.5 ml), and the mixture was stirred at 60°C for 1 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was recrystallized from ethanol-hexane to give (2E)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-nitropyridin-2-yl)oxy]phenyl}acrylic acid (383 mg) as pale-yellow crystals. The obtained crystal were dissolved in acetonitrile (10 ml), and 2-methyl-6-nitrobenzoic anhydride (411 mg), triethylamine (305 mg), 4-dimethylaminopyridine (126 mg) and pentane-1-sulfonamide (156 mg) were added, and the mixture was stirred

at room temperature for 24 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-nitropyridin-2-yl)oxy]phenyl}-N-(pentylsulfonyl)acrylamide (178 mg, yield: 35%) as colorless crystals. melting point 148.0-150.3°C.

Example 186

To a mixed solution of ethyl (2E)-3-(4-(2-methoxyethoxy)-2-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}phenyl)acrylate (483 mg) in tetrahydrofuran (12 ml) and ethanol (8 ml) was added a 1N aqueous sodium hydroxide solution (2.5 ml), and the mixture was stirred at room temperature for 5 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated to give (2E)-3-(4-(2-methoxyethoxy)-2-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}phenyl)acrylic acid (353 mg) as colorless crystals. The obtained crystals were dissolved in acetonitrile (10 ml), 2-methyl-6-nitrobenzoic anhydride (377 mg), triethylamine (280 mg), 4-dimethylaminopyridine (113 mg) and pentane-1-sulfonamide (139 mg) were added, and the mixture was stirred at room temperature for 24 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3, v/v) to give (2E)-3-(4-(2-methoxyethoxy)-2-{[6-

(trifluoromethyl)pyridazin-3-yl]oxy}phenyl)-N-(pentylsulfonyl)acrylamide (120 mg, yield: 20%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.87 (3 H, t, J = 7.1 Hz), 1.25 - 1.42 (4 H, m), 1.75 - 1.84 (2 H, m), 3.37 - 3.42 (2 H, m), 3.43 (3 H, s), 3.72 - 3.75 (2 H, m), 4.12 - 4.15 (2 H, m), 6.32 (1 H, d, J = 15.6 Hz), 6.77 (1 H, d, J = 2.4 Hz), 6.89 (1 H, dd, J = 9.0, 2.4 Hz), 7.45 (1 H, d, J = 9.0 Hz), 7.54 (1 H, d, J = 9.0 Hz), 7.76 (1 H, d, J = 15.6 Hz), 7.88 (1 H, d, J = 9.0 Hz), 8.32 (1 H, s).

Example 187

To a solution of (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (358 mg) in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (324 mg), triethylamine (275 mg), 4-dimethylaminopyridine (113 mg) and pentane-1-sulfonamide (138 mg), and the mixture was stirred at room temperature for 20 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-2-methyl-N-(pentylsulfonyl)acrylamide (421 mg, yield: 88%) as yellow crystals. melting point 97.0-98.0°C.

Example 188

To a solution of (2E)-2-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzylidene]butanoic acid (325 mg) in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (332 mg), triethylamine (247 mg), 4-dimethylaminopyridine (98 mg) and pentane-1-sulfonamide (130 mg), and the mixture was stirred at room temperature for 44

hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-2-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzylidene]-N-(pentylsulfonyl)butanamide (363 mg, yield: 84%) as colorless crystals. melting point 118.0-118.4°C.

Example 189

To a solution of (2E)-3-[2-[(2,4-dichlorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylic acid (304 mg) in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (359 mg), triethylamine (235 mg), 4-dimethylaminopyridine (99 mg) and pentane-1-sulfonamide (136 mg), and the mixture was stirred at room temperature for 20 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 2,4-dichloro-N-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenyl)benzamide (160 mg, yield: 40%) as colorless crystals. melting point 176.8-177.1°C.

Example 190

To a solution of (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(3-methoxypropoxy)phenyl]-2-methylacrylic acid (338 mg) in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (312 mg), triethylamine (265 mg), 4-dimethylaminopyridine (100 mg) and pentane-1-sulfonamide (130

mg), and the mixture was stirred at room temperature for 20 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(3-methoxypropoxy)phenyl]-2-methyl-N-(pentylsulfonyl)acrylamide (394 mg, yield: 84%) as yellow crystals. melting point 116.0-116.8°C.

Example 191

To a solution of (2E)-3-[2-[(2,4-difluorobenzoyl)amino]-4-(2-methoxyethoxy)phenyl]acrylic acid (366 mg) in acetonitrile (10 ml) were added 2-methyl-6-nitrobenzoic anhydride (369 mg), triethylamine (340 mg), 4-dimethylaminopyridine (120 mg) and pentane-1-sulfonamide (157 mg), and the mixture was stirred at room temperature for 24 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 2,4-difluoro-N-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenyl)benzamide (158 mg, yield: 32%) as colorless crystals. melting point 140.0-140.8°C.

Example 192

To a solution of (2E)-3-[2-({5-[(tert-butoxycarbonyl)amino]-3-methylpyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (256 mg) in acetonitrile (8 ml) were added 2-methyl-6-nitrobenzoic anhydride (244 mg),

triethylamine (180 mg), 4-dimethylaminopyridine (76 mg) and pentane-1-sulfonamide (99 mg), and the mixture was stirred at room temperature for 22 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give tert-butyl [6-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)-5-methylpyridin-3-yl]carbamate (288 mg, yield: 86%) as yellow crystals. melting point 149.5-150.2°C.

Example 193

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylic acid (7.90 g) in acetonitrile (30 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.51 g), 4-dimethylaminopyridine (2.59 g) and 1-pentanesulfonamide (2.19 g), and the mixture was stirred at room temperature for 16 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:4, v/v) to give (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)-N-(pentylsulfonyl)acrylamide (4.50 g, yield: 46%) as a white solid. Recrystallization from diisopropyl ether-hexane gave a white powder. melting point 106-108°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.89 (3 H, t, J = 7.2 Hz), 0.98 -

1.17 (21 H, m), 1.21 - 1.49 (4 H, m), 1.70 - 1.92 (2 H, m), 3.35 - 3.56 (2 H, m), 3.91 - 4.19 (4 H, m), 6.37 (1 H, d, J = 15.8 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.90 (1 H, dd, J = 8.7, 2.5 Hz), 7.60 (1 H, d, J = 8.9 Hz), 7.72 - 7.83 (2 H, m), 8.03 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.0, 0.9 Hz).

Example 194

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (252 mg) in pyridine (2 ml) was added acetic anhydride (0.088 ml) under ice-cooling, and the mixture was stirred for 1 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried, and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give 2-(3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)ethyl acetate (237 mg, yield: 87%) as white crystals. melting point 141-144°C.

Example 195

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]acrylic acid (0.79 g) in acetonitrile (6 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (541 mg), 4-dimethylaminopyridine (398 mg) and pentane-1-sulfonamide (269 mg), and the mixture was stirred at room temperature for 16 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column

chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:4, v/v) to give a white solid. Recrystallization from diethyl ether-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (202 mg, yield: 20%) as a white powder. melting point 126.5-128.5°C.

Example 196

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}acrylic acid (1.00 g) in acetonitrile (6 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (541 mg), 4-dimethylaminopyridine (398 mg) and pentane-1-sulfonamide (328 mg), and the mixture was stirred at room temperature for 16 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:4, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (194 mg, yield: 15%) as a white powder. melting point 116-118°C.

Example 197

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(pyrimidin-2-yloxy)phenyl]acrylic acid (1.00 g) in acetonitrile (12 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (782 mg), 4-dimethylaminopyridine (374 mg) and pentane-1-sulfonamide (295 mg), and the mixture was stirred at room temperature for 16 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric

acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:2, v/v) to give a white solid. Recrystallization from diethyl ether-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(pyrimidin-2-yloxy)phenyl]-N-(pentylsulfonyl)acrylamide (140 mg, yield: 12%) as a white powder. melting point 80.5-82.5°C.

Example 198

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}acrylic acid (831 mg) in acetonitrile (12 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (652 mg), 4-dimethylaminopyridine (312 mg) and pentane-1-sulfonamide (257 mg), and the mixture was stirred at room temperature for 16 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:20 - 1:4, v/v) to give a white solid. Recrystallization from diisopropyl ether-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (397 mg, yield: 38%) as a white powder. melting point 83-85.5°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.26 - 1.44 (7 H, m), 1.46 - 1.70 (4 H, m), 1.70 - 2.04 (4 H, m), 3.45 (3 H, s), 3.73 - 3.76 (2 H, m), 4.11 - 4.14 (2 H, m), 4.20 - 4.32 (3 H, m), 6.38 - 6.52 (3 H, m), 7.42 (1 H, d, J = 8.7 Hz), 7.93 (1 H, d, J = 16.2 Hz).

Recrystallization of the crude crystals obtained under the same conditions as in Example 198 from diethyl ether-

hexane gave crystals. The X-ray powder diffraction pattern of this crystal as measured using Cu-Kα ray (tube voltage: 40 KV; tube current: 50 mA) as a radiation source and RINT2100 type Ultima+ (Rigaku Corporation) is shown in Fig. 3.

Data (main peak) of X-ray powder diffraction

diffraction angle: 2θ (°)	spacing: d value (angstrom)
4.20	21.0
6.92	12.8
11.3	7.80
12.5	7.06
19.0	4.68
20.7	4.28
22.9	3.88
24.7	3.60

Example 199

A mixture of (2E)-3-(1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazol-5-yl)acrylic acid (220 mg), N,N'-carbonyldiimidazole (137 mg) and N,N-dimethylformamide (6.0 ml) was stirred at room temperature for 1 hr, pentane-1-sulfonamide (102 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (129 mg) were added, and the mixture was stirred at 100°C for 4 hr. After cooling to room temperature, the reaction mixture was poured into 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:2, v/v) to give (2E)-3-(1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-3-isopropoxy-1H-pyrazol-5-yl)-N-(pentylsulfonyl)acrylamide (30 mg, yield: 10%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (3 H, t, J = 7.2 Hz), 1.22 - 1.49 (10 H, m), 1.75 - 1.90 (2 H, m), 3.40 - 3.51 (2 H, m), 4.61 - 4.74 (1 H, m), 5.58 (2 H, s), 6.07 (1 H, s), 6.34 (1 H, d, J = 15.3 Hz), 7.62 (1 H, d, J = 15.3 Hz), 7.91 - 7.96 (1 H, m),

8.61 - 8.65 (1 H, m), 8.74 (1 H, m).

Example 200

Under ice-cooling, to a solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (9.03 g) in N,N-dimethylformamide (150 ml) was added sodium hydride (60% in oil, 2.28 g), and the mixture was stirred under an argon atmosphere at room temperature for 30 min. The reaction mixture was ice-cooled again, a solution of 1-(2,4-dichlorobenzyl)-3-(methoxymethoxy)-1H-pyrazole-5-carbaldehyde (4.80 g) in N,N-dimethylformamide (40 ml) was added, and the mixture was stirred under an argon atmosphere at 0°C for 1 hr. The reaction mixture was poured into a saturated sodium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (1:9 - 2:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give tert-butyl ({(E)-2-[1-(2,4-dichlorobenzyl)-3-(methoxymethoxy)-1H-pyrazol-5-yl]vinyl}sulfonyl)carbamate (3.16 g, yield: 42%) as colorless crystals. melting point 139-140°C.

Example 201

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (1.00 g) in tetrahydrofuran (25 ml) was added N,N'-carbonyldiimidazole (604 mg), and the mixture was heated under reflux for 1 hr. After allowing to cool to room temperature, 3-methoxypropane-1-sulfonamide (0.57 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.70 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried (MgSO4), filtrated and concentrated. The obtained residue was subjected

to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 - 9:1, v/v) to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(3-methoxypropyl)sulfonyl]acrylamide (138 mg, yield: 10%) as a white amorphous form.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.01 - 2.16 (2 H, m), 3.30 (3 H, s), 3.44 (3 H, s), 3.47 (2 H, t, J = 5.9 Hz), 3.54 - 3.64 (2 H, m), 3.70 - 3.82 (2 H, m), 4.06 - 4.20 (2 H, m), 6.38 (1 H, d, J = 15.6 Hz), 6.68 - 6.76 (1 H, m), 6.91 (1 H, dd, J = 8.8, 2.5 Hz), 7.60 (1 H, d, J = 8.9 Hz), 7.79 (1 H, d, J = 15.6 Hz), 8.03 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Example 202

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propanoic acid (0.50 g) in tetrahydrofuran (15 ml) was added N,N'-carbonyldiimidazole (340 mg), and the mixture was heated under reflux for 1 hr. After allowing to cool to room temperature, 3-methoxypropane-1-sulfonamide (0.31 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.40 ml) were added to the reaction mixture, and the mixture was stirred overnight. The reaction mixture was concentrated and the concentrate was dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-[(3-methoxypropyl)sulfonyl]propanamide (4.12 g, yield: 99%) as white crystals. melting point 114-115°C.

Example 203

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]propan-1-ol (499 mg) in dichloromethane (5 ml) was added chlorosulfonylisocyanate (0.15 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture and the mixture was stirred for 1 hr. 3-Methyl-1-butylamine (0.40 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane then from ethanol-water gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(3-methylbutyl)amino]sulfonyl}carbamate (85 mg, yield: 12%) as white crystals. melting point 123.0-123.5°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.0 Hz), 1.84 - 2.00 (2 H, m), 2.56 (2 H, t, J = 7.4 Hz), 3.15 - 3.27 (2 H, m), 3.44 (3 H, s), 3.53 (2 H, t, J = 5.2 Hz), 3.55 - 3.62 (1 H, m), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.09 (2 H, dd, J = 5.5, 4.0 Hz), 4.14 (2 H, t, J = 6.3 Hz), 5.40 (1 H, t, J = 5.8 Hz), 6.68 (1 H, d, J = 2.6 Hz), 6.83 (1 H, dd, J = 8.5, 2.6 Hz), 7.19 (1 H, d, J = 8.7 Hz), 7.47 (1 H, s), 8.01 (1 H, d, J = 2.1 Hz), 8.27 (1 H, dd, J = 2.1, 0.9 Hz).

Example 204

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (497 mg) in dichloromethane (5 ml) was added chlorosulfonylisocyanate (0.15 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Isopropoxyethylamine (0.40 ml) was added, and the mixture was stirred overnight at room

temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (730 mg, yield: 97%) as white crystals. melting point 113.5-114.0°C.

Recrystallization of the crude crystals obtained under the same conditions as in Example 204 from ethanol-hexane gave crystals. The X-ray powder diffraction pattern of this crystal as measured using Cu-$K\alpha$ ray (tube voltage: 40 KV; tube current: 50 mA) as a radiation source and RINT2100 type Ultima+ (Rigaku Corporation) is shown in Fig. 4.

Data (main peak) of X-ray powder diffraction

diffraction angle: 2θ (°)	spacing: d value (angstrom)
7.74	11.4
11.0	8.01
15.5	5.70
18.7	4.75
20.8	4.27
23.9	3.72
27.5	3.24

Example 205

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (495 mg) in N,N-dimethylformamide (5 ml) was added N,N'-carbonyldiimidazole (296 mg), and the mixture was stirred at 40°C for 1 hr. After allowing to cool to room temperature, N-(4-methylcyclohexyl)sulfamide (254 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. 1N

Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(4-methylcyclohexyl)amino]sulfonyl}carbamate (323 mg, yield: 43%) as white crystals. melting point 121.5-121.8°C.

Example 206

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (504 mg) in dichloromethane (5 ml) was added chlorosulfonylisocyanate (0.15 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Phenylethylamine (0.40 ml) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenylethyl)amino]sulfonyl}carbamate (596 mg, yield: 76%) as white crystals. melting point 110-113°C.

Example 207

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

methoxyethoxy)phenyl]propan-1-ol (493 mg) in N,N-dimethylformamide (5 ml) was added N,N'-carbonyldiimidazole (291 mg), and the mixture was stirred at 40°C for 1 hr. After allowing to cool to room temperature, N-[2-(2-thienyl)ethyl]sulfamide (275 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 ml) were added to the reaction mixture, and the mixture was stirred overnight. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow solid. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate (319 mg, yield: 41%) as white crystals. melting point 117.5-118.0°C.

Example 208

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (483 mg) in dichloromethane (5 ml) was added chlorosulfonylisocyanate (0.15 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Pyridin-2-ylethylamine (0.40 g) was added, and the mixture was stirred overnight at room temperature. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 9:1, v/v) to give a white solid. Recrystallization from ethyl

acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (439 mg, yield: 58%) as a white powder. melting point 91-93°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.78 - 1.97 (2 H, m), 2.53 (2 H, t, J = 7.4 Hz), 3.06 (2 H, t, J = 6.2 Hz), 3.43 (3 H, s), 3.52 (2 H, t, J = 6.2 Hz), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 3.98 - 4.15 (4 H, m), 6.37 (1 H, br. s.), 6.67 (1 H, d, J = 2.4 Hz), 6.81 (1 H, dd, J = 8.5, 2.6 Hz), 7.09 - 7.21 (3 H, m), 7.61 (1 H, ddd, J = 7.6, 7.6, 1.9 Hz), 7.99 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz), 8.49 (1 H, dd, J = 5.1, 1.9 Hz).

Recrystallization of the crude crystals obtained under the same conditions as in Example 208 from ethyl acetate-hexane gave crystals. The X-ray powder diffraction pattern of this crystal as measured using Cu-Kα ray (tube voltage: 40 KV; tube current: 50 mA) as a radiation source and RINT2100 type Ultima+ (Rigaku Corporation) is shown in Fig. 5.

Data (main peak) of X-ray powder diffraction

diffraction angle: 2θ (°)	spacing: d value (angstrom)
9.44	9.36
12.7	6.94
14.4	6.13
15.9	5.56
17.3	5.12
20.1	4.42
20.7	4.30
22.7	3.91
23.7	3.75

Example 209

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylpropanoic acid (495 mg) in dichloromethane (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (242 mg), 4-dimethylaminopyridine (252 mg) and pentane-1-sulfonamide (243 mg), and the mixture was stirred overnight at room temperature.

1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-N-(pentylsulfonyl)propanamide as white crystals. melting point 136.5-138.0°C.

Example 210

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoic acid (512 mg) in dichloromethane (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (269 mg), 4-dimethylaminopyridine (278 mg) and pentane-1-sulfonamide (266 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 65:35, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. The obtained crystals were subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxy-N-(pentylsulfonyl)propanamide (154 mg, yield: 23%) as white crystals. melting point 76.0-78.0°C.

Example 211

To a solution of (2E)-3-[2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (220 mg) in dichloromethane (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (201 mg), 4-dimethylaminopyridine (299 mg) and pentane-1-sulfonamide (106 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-N-(pentylsulfonyl)acrylamide (158 mg, yield: 55%) as white crystals. melting point 108-111°C.

Example 212

To a solution of N-(aminosulfonyl)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanamide (201 mg) in tetrahydrofuran (20 ml) were added triphenylphosphine (143 mg), 1-butanol (0.10 ml) and a diethyl azodicarboxylate 40%-toluene solution (0.30 ml) under ice-cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v) to give a white solid. This was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to ethyl acetate alone) to give a white solid. Recrystallization from ethyl acetate-hexane gave N-(aminosulfonyl)-N-butyl-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanamide (30 mg, yield: 13%) as white crystals. melting point 102-103°C.

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Example 213

To a solution of N-(aminosulfonyl)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanamide (201 mg) in tetrahydrofuran (20 ml) were added triphenylphosphine (143 mg), 2-methoxyethanol (0.10 ml) and a diethyl azodicarboxylate 40%-toluene solution (0.30 ml) under ice-cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the obtained residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:19 - 65:35, v/v) to give a white solid. This was subjected to basic silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 to ethyl acetate alone, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave N-(aminosulfonyl)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(2-methoxyethyl)propanamide (65 mg, yield: 29%) as white crystals. melting point 101.0-101.1°C.

Example 214

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanoic acid (507 mg) in acetonitrile (6 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.25 g), 4-dimethylaminopyridine (335 mg) and N-pentylsulfamide (202 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 9:1, v/v) to give a white solid. The obtained solid was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:4, v/v) to give a white

solid. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(pentylamino)sulfonyl]propanamide (14 mg, yield: 2%) as white crystals. melting point 153.0-153.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.93 (3 H, m), 1.20 - 1.37 (4 H, m), 1.47 (2 H, tt, J = 7.3, 7.2 Hz), 2.57 (2 H, t, J = 7.2 Hz), 2.71 (2 H, q, J = 6.8 Hz), 2.92 (2 H, t, J = 7.3 Hz), 3.42 (3 H, s), 3.68 - 3.74 (2 H, m), 4.03 - 4.08 (2 H, m), 4.99 (1 H, t, J = 6.3 Hz), 6.55 (1 H, d, J = 2.4 Hz), 6.78 (1 H, dd, J = 8.5, 2.4 Hz), 7.19 (1 H, d, J = 8.5 Hz), 8.07 (1 H, d, J = 2.3 Hz), 8.35 (1 H, dd, J = 2.0, 0.8 Hz), 8.76 (1 H, s).

Example 215

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (837 mg) in acetonitrile (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (515 mg), 4-dimethylaminopyridine (385 mg) and N-pentylsulfamide (336 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 7:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. The crystals were recrystallized from ethanol-water to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(pentylamino)sulfonyl]acrylamide (104 mg, yield: 9%) as white crystals. melting point 120-122°C.

Example 216

To a solution of (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (300 mg) in dichloromethane (10 ml) were added 1-ethyl-3-(3-

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dimethylaminopropyl)carbodiimide (0.20 g), 4-dimethylaminopyridine (236 mg) and pentane-1-sulfonamide (115 mg), and the mixture was stirred under ice-cooling for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (139 mg, yield: 35%) as white crystals. melting point 104-106°C.

Example 217

To a solution of (2E)-3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylic acid (789 mg) in acetonitrile (6 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (356 mg), 4-dimethylaminopyridine (209 mg) and pentane-1-sulfonamide (176 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give (2E)-3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-N-(pentylsulfonyl)acrylamide (515 mg, yield: 54%) as a colorless solid. Recrystallization from ethyl acetate-hexane gave white crystal as dihydrate. melting point 108.0-108.5°C.

Example 218

To a solution of (2E)-3-(4-(2-{[tert-

butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-N-(pentylsulfonyl)acrylamide (490 mg) in tetrahydrofuran (6 ml) was added a tetra-n-butylammonium fluoride 1.0M-tetrahydrofuran solution (1.20 ml), and the mixture was stirred at 50°C for 20 min. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (15:85 to ethyl acetate alone, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide monohydrate (234 mg, yield: 69%) as white crystals. melting point 112.5-112.8°C.

Example 219

To a solution of ethyl (2E)-3-[2-(4-aminophenoxy)-4-(2-methoxyethoxy)phenyl]acrylate (0.92 g) in acetonitrile (10 ml) were added cupric chloride (513 mg) and t-butyl nitrite (0.45 ml) under ice-cooling, and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 28%w/w ammonia water, water and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v). The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 2:3, v/v) to give an orange oil.

To a solution of the obtained oil in tetrahydrofuran (1 ml) and ethanol (1 ml) was added a 1N aqueous sodium hydroxide solution (2.5 ml), and the mixture was stirred at 50°C for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid (2.5 ml) was added to the reaction mixture,

and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtrated and concentrated.

To a solution of obtained residue in acetonitrile (2 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (339 mg), 4-dimethylaminopyridine (208 mg) and pentane-1-sulfonamide (142 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 1:1, v/v) to give a colorless oil. The obtained residue was subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give 3-[2-(4-chlorophenoxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)propanamide hemihydrate (30 mg, yield: 2%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.83 - 0.92 (3 H, m), 1.21 - 1.41 (4 H, m), 1.65 - 1.78 (2 H, m), 2.61 (2 H, t, J = 7.4 Hz), 2.91 (2 H, t, J = 7.4 Hz), 3.26 - 3.37 (2 H, m), 3.41 (3 H, s), 3.69 (2 H, dd, J = 5.5, 3.8 Hz), 4.01 (2 H, dd, J = 5.6, 3.9 Hz), 6.43 (1 H, d, J = 2.4 Hz), 6.61 - 6.72 (1 H, m), 6.86 - 6.93 (2 H, m), 7.16 (1 H, d, J = 8.5 Hz), 7.26 - 7.32 (2 H, m).

Then, a pale-yellow solid was obtained. Recrystallization from ethyl acetate-diisopropyl ether gave 3-[4-(2-methoxyethoxy)-2-phenoxyphenyl]-N-(pentylsulfonyl)propanamide (44 mg, yield: 4%) as white crystals. melting point 70.4-70.5°C.

Example 220

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (409 mg) in acetonitrile (10 ml) were added

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (311 mg), 4-dimethylaminopyridine (198 mg) and N-(2-phenylethyl)sulfamide (195 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-{[(2-phenylethyl)amino]sulfonyl}acrylamide (246 mg, yield: 42%) as white crystals. melting point 147.0-147.5°C.

Example 221

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (216 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (154 mg), 4-dimethylaminopyridine (102 mg) and N-(3-methoxypropyl)sulfamide (102 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-hexane gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-{[(3-methoxypropyl)amino]sulfonyl}-2-methylacrylamide (79 mg, yield: 27%) as white crystals. melting point 120.0-121.0°C.

Example 222

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (215 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (155 mg), 4-dimethylaminopyridine (108 mg) and N-(2-isopropoxyethyl)sulfamide (106 mg), and the mixture was stirred

overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-hexane gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-{[(2-isopropoxyethyl)amino]sulfonyl}-2-methylacrylamide (160 mg, yield: 54%) as white crystals. melting point 137.5-137.7°C.

Example 223

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (210 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (170 mg), 4-dimethylaminopyridine (110 mg) and N-(4-methylcyclohexyl)sulfamide (88 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-{[(4-methylcyclohexyl)amino]sulfonyl}acrylamide (130 mg, yield: 49%) as white crystals. melting point 176.8-177.2°C.

Example 224

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (218 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (161 mg), 4-dimethylaminopyridine (107 mg) and N-pentylsulfamide (75 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl

acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-[(pentylamino)sulfonyl]acrylamide (176 mg, yield: 69%) as white crystals. melting point 137.8-138.5°C.

Example 225

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (210 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (159 mg), 4-dimethylaminopyridine (112 mg) and N-[2-(2-thienyl)ethyl]sulfamide (89 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-({[2-(2-thienyl)ethyl]amino}sulfonyl)acrylamide (181 mg, yield: 69%) as white crystals. melting point 130-131°C.

Example 226

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (220 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (172 mg), 4-dimethylaminopyridine (117 mg) and N-pentylsulfamide (74 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from

ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-N-[(pentylamino)sulfonyl]acrylamide (167 mg, yield: 65%) as white crystals. melting point 152.5-153.0°C.

Example 227

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (218 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (163 mg), 4-dimethylaminopyridine (109 mg) and N-(3-methoxypropyl)sulfamide (102 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-{[(3-methoxypropyl)amino]sulfonyl}-2-methylacrylamide (83 mg, yield: 28%) as white crystals. melting point 121-122°C.

Example 228

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (420 mg) in acetonitrile (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (276 mg), 4-dimethylaminopyridine (167 mg) and N-(2-phenylethyl)sulfamide (188 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave white crystals.

Recrystallization from ethanol-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-{[(2-phenylethyl)amino]sulfonyl}acrylamide (75 mg, yield: 13%) as white crystals. melting point 85.0-85.5°C.

Example 229

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (419 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (304 mg), 4-dimethylaminopyridine (193 mg) and 4-chlorobenzenesulfonamide (174 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-N-[(4-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylamide (386 mg, yield: 72%) as white crystals. melting point 182.0-182.5°C.

Example 230

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (270 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (181 mg), 4-dimethylaminopyridine (114 mg) and 4-chlorobenzenesulfonamide (114 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-N-[(4-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-

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methoxyethoxy)phenyl]-2-methylacrylamide (194 mg, yield: 54%) as white crystals. melting point 145.7-145.8°C.

Example 231

To a solution of (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (216 mg) in acetonitrile (2.5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (163 mg), 4-dimethylaminopyridine (143 mg) and N-(tetrahydrofuran-2-ylmethyl)sulfamide (106 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-hexane gave (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-{[(tetrahydrofuran-2-ylmethyl)amino]sulfonyl}acrylamide (119 mg, yield: 39%) as white crystals. melting point 125.3-126.5°C.

Example 232

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (424 mg) in acetonitrile (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (319 mg), 4-dimethylaminopyridine (218 mg) and 3-chlorobenzenesulfonamide (191 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-N-[(3-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylamide (587 mg, yield: 100%) as white crystals. melting point 157.0-158.0°C.

Example 233

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (446 mg) in acetonitrile (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (327 mg), 4-dimethylaminopyridine (192 mg) and 3-chlorobenzenesulfonamide (179 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-N-[(3-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylamide (250 mg, yield: 44%) as white crystals. melting point 89-92°C.

Example 234

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (845 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (635 mg), 4-dimethylaminopyridine (331 mg) and 4-(trifluoromethyl)benzenesulfonamide (446 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-{[4-(trifluoromethyl)phenyl]sulfonyl}acrylamide (794 mg, yield: 64%) as white crystals. melting point 186.3-186.5°C.

Example 235

To a solution of (2E)-3-[2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (834 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (516 mg), 4-dimethylaminopyridine (331 mg) and 2-chlorobenzenesulfonamide (383 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-N-[(2-chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylamide (822 mg, yield: 70%) as white crystals. melting point 168-169°C.

Example 236

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (833 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (529 mg), 4-dimethylaminopyridine (343 mg) and p-toluenesulfonamide (372 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(4-methylphenyl)sulfonyl]acrylamide (831 mg, yield: 73%) as white crystals. melting point 102.5-106.5°C.

Example 237

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (843 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (629 mg), 4-dimethylaminopyridine (346 mg) and 4-fluorobenzenesulfonamide (350 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(4-fluorophenyl)sulfonyl]acrylamide (670 mg, yield: 58%) as white crystals. melting point 183.0-184.0°C.

Example 238

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (843 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (600 mg), 4-dimethylaminopyridine (352 mg) and benzenesulfonamide (307 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(phenylsulfonyl)acrylamide (774 mg, yield: 71%) as white crystals. melting point 135.5-136.0°C.

Example 239

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (206 mg) in acetonitrile (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (276 mg), 4-dimethylaminopyridine (97 mg) and 2-pyridinesulfonamide (71 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added

to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pyridin-2-ylsulfonyl)acrylamide (36 mg, yield: 13%) as white mica crystals. melting point 164.0-165.0°C.

Example 240

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (846 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (620 mg), 4-dimethylaminopyridine (339 mg) and 3-pyridinesulfonamide (314 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pyridin-3-ylsulfonyl)acrylamide (557 mg, yield: 51%) as white crystals. melting point 165-167°C.

Example 241

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (851 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (573 mg), 4-dimethylaminopyridine (336 mg) and m-toluenesulfonamide (375 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated

and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(3-methylphenyl)sulfonyl]acrylamide (737 mg, yield: 63%) as white crystals. melting point 147.0-147.5°C.

Example 242

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (837 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (625 mg), 4-dimethylaminopyridine (339 mg) and 3-cyanobenzenesulfonamide (369 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(3-cyanophenyl)sulfonyl]acrylamide (931 mg, yield: 80%) as white crystals. melting point 195-197°C.

Example 243

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (837 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (632 mg), 4-dimethylaminopyridine (332 mg) and trifluoromethanesulfonamide (306 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-

N-[(trifluoromethyl)sulfonyl]acrylamide (428 mg, yield: 39%) as white crystals. melting point 125.5-128.0°C.

Example 244

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (860 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (795 mg), 4-dimethylaminopyridine (316 mg) and 2,2,2-trifluoroethanesulfonamide (320 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-N-[(2,2,2-trifluoroethyl)sulfonyl]acrylamide (905 mg, yield: 80%) as white crystals. melting point 159.0-159.5°C.

Example 245

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (871 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (814 mg), 4-dimethylaminopyridine (355 mg) and trifluoromethanesulfonamide (305 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-N-[(trifluoromethyl)sulfonyl]acrylamide (980 mg, yield: 86%) as white crystals. melting point 146.0-147.0°C.

Example 246

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (840 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (634 mg), 4-dimethylaminopyridine (370 mg) and 2,2,2-trifluoroethanesulfonamide (324 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethanol-water gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(2,2,2-trifluoroethyl)sulfonyl]acrylamide (847 mg, yield: 76%) as white crystals. melting point 146.0-147.5°C.

Example 247

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]phenyl}acrylic acid (474 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (373 mg), 4-dimethylaminopyridine (186 mg) and pentane-1-sulfonamide (144 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the resulting solid was collected by filtration and washed with water to give white solid. Recrystallization from ethanol-water gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]phenyl}-N-(pentylsulfonyl)acrylamide (326 mg, yield: 56%) as white crystals. melting point 194-196°C.

Example 248

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-3-methylbutoxy)phenyl]acrylic acid (446 mg) in acetonitrile (5

ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (360 mg), 4-dimethylaminopyridine (230 mg) and pentane-1-sulfonamide (150 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-hydroxy-3-methylbutoxy)phenyl]-N-(pentylsulfonyl)acrylamide (242 mg, yield: 42%) as white crystals. melting point 135.5-136.0°C.

Example 249

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methoxymethoxy)-1,1-dimethylpropoxy]phenyl}acrylate (975 mg) in tetrahydrofuran (2.5 ml) and ethanol (2.5 ml) was added a 1N aqueous sodium hydroxide solution (5.0 ml), and the mixture was stirred at 50°C for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid (5.0 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale-yellow oil.

To a solution of the obtained oil in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (767 mg), 4-dimethylaminopyridine (293 mg) and pentane-1-sulfonamide (262 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), filtrated and concentrated.

The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v). The obtained residue was subjected to reversed-phase high performance liquid chromatography, and eluted with acetonitrile-water (2:3 to acetonitrile alone, v/v) to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methoxymethoxy)-1,1-dimethylpropoxy]phenyl}-N-(pentylsulfonyl)acrylamide (222 mg, yield: 21%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.73 - 0.97 (3 H, m), 1.18 - 1.36 (4 H, m), 1.38 (6 H, s), 1.65 - 1.89 (2 H, m), 2.03 (2 H, t, J = 7.1 Hz), 3.35 (3 H, s), 3.37 - 3.54 (2 H, m), 3.74 (2 H, t, J = 7.2 Hz), 4.61 (2 H, s), 6.45 (1 H, d, J = 15.6 Hz), 6.77 (1 H, d, J = 2.3 Hz), 6.93 (1 H, d, J = 8.3 Hz), 7.58 (1 H, d, J = 8.7 Hz), 7.80 (1 H, d, J = 15.6 Hz), 7.92 - 8.08 (1 H, m), 8.18 - 8.29 (1 H, m).

Example 250

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]acrylic acid (3.62 g) in acetonitrile (40 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.21 g), 4-dimethylaminopyridine (1.54 g) and pentane-1-sulfonamide (1.27 g), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 1:1, v/v). The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 1:1, v/v). The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 9:1, v/v). The residue was triturated with diisopropyl ether to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-

2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]-N-(pentylsulfonyl)acrylamide 0.10 diisopropyl ether-0.19 ethyl acetate complex (424 mg, yield: 9%) as a white solid. Recrystallization from acetone-hexane gave white crystals as 0.23 acetone solvate. melting point 98-100°C.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.94 (3 H, m), 1.21 - 1.45 (4 H, m), 1.34 (6 H, s), 1.70 - 1.92 (2 H, m), 2.08 (1 H, s), 3.23 - 3.56 (2 H, m), 3.82 (2 H, s), 6.38 (1 H, d, J = 15.4 Hz), 6.71 (1 H, d, J = 2.5 Hz), 6.91 (1 H, dd, J = 8.8, 2.5 Hz), 7.61 (1 H, d, J = 8.8 Hz), 7.78 (1 H, d, J = 15.4 Hz), 8.03 (1 H, d, J = 2.2 Hz), 8.25 (1 H, dd, J = 2.2, 0.8 Hz).

Example 251

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylic acid (439 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (356 mg), 4-dimethylaminopyridine (206 mg) and pentane-1-sulfonamide (151 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-N-(pentylsulfonyl)acrylamide (149 mg, yield: 26%) as white crystals. melting point 116.5-118.0°C.

Example 252

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoic acid (1.21 g) in tetrahydrofuran (25 ml) was added N,N'-carbonyldiimidazole (877 mg), and the mixture was heated under reflux for 1 hr. After allowing to cool to

room temperature, pentane-1-sulfonamide (817 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.80 ml) were added to the reaction mixture, and the mixture was stirred for 3 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (hexane alone to 2:3, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethyl-N-(pentylsulfonyl)propanamide (1.51 g, yield: 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.82 - 0.95 (3 H, m), 1.25 (6 H, s), 1.28 - 1.48 (4 H, m), 1.75 (2 H, tt, J = 7.6, 7.6 Hz), 2.76 (2 H, s), 3.34 - 3.42 (2 H, m), 3.43 (3 H, s), 3.73 (2 H, dd, J = 5.4, 3.9 Hz), 4.09 (2 H, dd, J = 5.5, 4.0 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.82 (1 H, dd, J = 8.7, 2.6 Hz), 7.20 (1 H, d, J = 8.7 Hz), 7.82 (1 H, br. s.), 8.01 (1 H, d, J = 2.3 Hz), 8.28 (1 H, dd, J = 2.1, 0.9 Hz).

Example 253

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethyl-N-(pentylsulfonyl)propanamide (1.23 g) in methanol (2 ml) was added a 1N aqueous sodium hydroxide solution (2.12 ml) at room temperature, and the reaction mixture was concentrated. The obtained residue was washed with cold methanol to give sodium {3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoyl}(pentylsulfonyl)azanide (982 mg, yield: 77%) as white crystals. melting point 190.5-191.0°C.

Example 254

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}acrylic acid (2.45 g) in

acetonitrile (50 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.97 g), 4-dimethylaminopyridine (1.26 g) and pentane-1-sulfonamide (788 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}-N-(pentylsulfonyl)acrylamide (1.70 g, yield: 54%) as white crystals. melting point 103.0-105.0°C.

Example 255

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}-N-(pentylsulfonyl)acrylamide (569 mg) in tetrahydrofuran (10 ml) and methanol (10 ml) was added a palladium-activated carbon ethylenediamine complex (61 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 12.5 hr. The reaction mixture was filtrated, and the filtrate was concentrated. The obtained residue was dissolved in tetrahydrofuran (10 ml) and methanol (10 ml), a palladium-activated carbon ethylenediamine complex (131 mg) was added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtrated and the filtrate was concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. The obtained crystals were subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 2:3, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(2-methoxyethoxy)propoxy]phenyl}-N-(pentylsulfonyl)propanamide (8 mg, yield: 1%) as white crystals. melting point 95.0-95.8°C.

Example 256

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}acrylic acid (1.86 g) in acetonitrile (50 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.55 g), 4-dimethylaminopyridine (0.99 g) and pentane-1-sulfonamide (611 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (1.01 g, yield: 42%) as white crystals. melting point 81.0-83.0°C.

Example 257

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (280 mg) in tetrahydrofuran (10 ml) and methanol (10 ml) was added a palladium-activated carbon ethylenediamine complex (60 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 8 hr. The reaction mixture was filtrated and the filtrate was concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave white crystals. The obtained crystals were subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 3:2, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-N-(pentylsulfonyl)propanamide (26 mg, yield: 9%) as white crystals. melting point 76.0-77.5°C.

Example 258

To a solution of 3-[2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propanoic acid (437 mg) in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (403 mg), 4-dimethylaminopyridine (179 mg) and pentane-1-sulfonamide (153 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane, then from ethanol-water gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-N-(pentylsulfonyl)propanamide (351 mg, yield: 62%) as white crystals. melting point 115.0-115.2°C.

Example 259

To a solution of ethyl (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(cyclopropylmethoxy)propoxy]phenyl}acrylate (0.66 g) in tetrahydrofuran (3 ml) and ethanol (3 ml) was added a 1N aqueous sodium hydroxide solution (4 ml), and the mixture was stirred at 50°C for 1 hr. After allowing to cool to room temperature, 1N hydrochloric acid (4 ml) was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a pale yellow oil.

To a solution of the obtained oil in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (415 mg), 4-dimethylaminopyridine (269 mg) and pentane-1-sulfonamide (164 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and

concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 1:1, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(cyclopropylmethoxy)propoxy]phenyl}-N-(pentylsulfonyl)acrylamide (301 mg, yield: 46%) as white crystals. melting point 124-125°C.

Example 260

To a solution of (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)-3-methylphenyl]acrylic acid (86 mg) in acetonitrile (5 ml) were added triethylamine (59 μl) and 2-methyl-6-nitrobenzoic anhydride (109 mg) under ice-cooling, and the mixture was stirred for 30 min. Then, 4-dimethylaminopyridine (51 mg) and pentane-1-sulfonamide (32 mg) were added, and the mixture was stirred overnight while allowing to warm to room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-[2-[(2,4-dichlorobenzyl)oxy]-4-(2-methoxyethoxy)-3-methylphenyl]-N-(pentylsulfonyl)acrylamide monohydrate (37 mg, yield: 32%) as white crystals. melting point 149-152°C.

In Example 261-Example 423, for the reversed-phase preparative HPLC, a UniPoint system equipped with YMC CombiPrep Pro C18, 50x20 mm, S-5 μm column (Gilson) was used and the mixtures were eluted with 0.1% trifluoroacetic acid-containing acetonitrile-water (5:95-100:0, v/v).

Example 261

A solution of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (30 mg) in dichloromethane (0.50 ml) was cooled to 0°C, a solution of chlorosulfonylisocyanate (12.5 mg) in dichloromethane (0.50

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ml) was added and the mixture was stirred for 30 min. A solution of pyridine (19.0 mg) in dichloromethane (0.50 ml) was added to the reaction mixture and the mixture was further stirred at 0°C for 30 min. A solution of isopropylamine (14.2 mg) in dichloromethane (0.50 ml) was added and the mixture was further stirred overnight while raising the temperature to room temperature. The reaction mixture was extracted with dichloromethane (3.0 ml) and water (2.0 ml), fractionated using a PTFE tube (polytetrafluoroethylene film processing tube, manufactured by Whatman) and the dichloromethane layer was concentrated. The residue was dissolved in DMSO (0.50 ml) and purified by reversed-phase preparative HPLC. 5% Aqueous sodium hydrogencarbonate solution (1.0 ml) was added to the object fraction and the mixture was concentrated. Water (1.0 ml) was added to the residue, and the mixture was extracted with ethyl acetate (3.5 ml) and fractionated by Presep™dehydrating (manufactured by Wako Pure Chemical Industries, Ltd.). The aqueous layer was extracted with ethyl acetate (3.5 ml). The ethyl acetate layers were combined, and the mixture was concentrated with a nitrogen blowing apparatus to give 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(isopropylamino)sulfonyl]carbamate (25 mg, yield: 57%). LC-MS purity: 100%, m/z=540[M-H$^+$], retention time=1.89 min.

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.06 (6 H, d, J = 6.4 Hz), 3.38 - 3.47 (1 H, m), 3.42 (3 H, s), 3.69 - 3.75 (2 H, m), 4.05 - 4.13 (2 H, m), 4.99 - 5.10 (3 H, m), 6.67 (1 H, d, J = 2.0 Hz), 6.82 (1 H, d, J = 6.6 Hz), 7.41 (1 H, d, J = 8.6 Hz), 7.97 (1 H, d, J = 1.7 Hz), 8.23 (1 H, s).

In the same manner as in Example 261, alcohols of [2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol, 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol, 3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propan-1-ol, 3-[2-(cyclopropylmethoxy)-4-

(2-methoxyethoxy)phenyl]propan-1-ol and 3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propan-1-ol were reacted with various amines to give the compounds of Example 262-Example 423.

Example 262

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-hydroxyethyl)amino]sulfonyl}carbamate

yield: 33%, LC-MS purity: 100%, m/z=542[M-H$^+$], retention time=1.68 min.

Example 263

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-cyanoethyl)amino]sulfonyl}carbamate

yield: 55%, LC-MS purity: 95%, m/z=551[M-H$^+$], retention time=1.73 min.

Example 264

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(tert-butylamino)sulfonyl]carbamate

yield: 50%, LC-MS purity: 95%, m/z=554[M-H$^+$], retention time=1.95 min.

Example 265

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(3-hydroxypropyl)amino]sulfonyl}carbamate

yield: 16%, LC-MS purity: 100%, m/z=556[M-H$^+$], retention time=1.71 min.

Example 266

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-methoxyethyl)amino]sulfonyl}carbamate

yield: 58%, LC-MS purity: 100%, m/z=556[M-H$^+$], retention time=1.77 min.

Example 267

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(cyclopentylamino)sulfonyl]carbamate

yield: 30%, LC-MS purity: 95%, m/z=566[M-H$^+$], retention time=1.95 min.

Example 268

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(1-ethylpropyl)amino]sulfonyl}carbamate
yield: 55%, LC-MS purity: 100%, m/z=568[M-H$^+$], retention time=2.01 min.

Example 269

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(3-methylbutyl)amino]sulfonyl}carbamate
yield: 52%, LC-MS purity: 100%, m/z=568[M-H$^+$], retention time=1.98 min.

Example 270

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(1,2-dimethylpropyl)amino]sulfonyl}carbamate
yield: 56%, LC-MS purity: 100%, m/z=568[M-H$^+$], retention time=2.00 min.

Example 271

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(1-methylbutyl)amino]sulfonyl}carbamate
yield: 58%, LC-MS purity: 100%, m/z=568[M-H$^+$], retention time=2.00 min.

Example 272

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(4-hydroxybutyl)amino]sulfonyl}carbamate
yield: 22%, LC-MS purity: 100%, m/z=570[M-H$^+$], retention time=1.74 min.

Example 273

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(cyclohexylamino)sulfonyl]carbamate
yield: 19%, LC-MS purity: 100%, m/z=580[M-H$^+$], retention time=2.00 min.

Example 274

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(tetrahydrofuran-2-ylmethyl)amino]sulfonyl}carbamate

yield: 54%, LC-MS purity: 100%, m/z=582[M-H$^+$], retention time=1.81 min.

Example 275

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(1,3-dimethylbutyl)amino]sulfonyl}carbamate

yield: 57%, LC-MS purity: 100%, m/z=582[M-H$^+$], retention time=2.05 min.

Example 276

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[2-(acetylamino)ethyl]amino}sulfonyl)carbamate

yield: 23%, LC-MS purity: 100%, m/z=583[M-H$^+$], retention time=1.67 min.

Example 277

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

yield: 62%, LC-MS purity: 100%, m/z=584[M-H$^+$], retention time=1.88 min.

Example 278

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[1-(methoxymethyl)propyl]amino}sulfonyl)carbamate

yield: 59%, LC-MS purity: 93%, m/z=584[M-H$^+$], retention time=1.91 min.

Example 279

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(3-ethoxypropyl)amino]sulfonyl}carbamate

yield: 57%, LC-MS purity: 100%, m/z=584[M-H$^+$], retention time=1.87 min.

Example 280

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[3-(methylthio)propyl]amino}sulfonyl)carbamate

yield: 67%, LC-MS purity: 100%, m/z=586[M-H$^+$], retention time=1.88 min.

Example 281

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(benzylamino)sulfonyl]carbamate

yield: 46%, LC-MS purity: 100%, m/z=588[M-H$^+$], retention time=1.91 min.

^{1}H-NMR (400 MHz, $CDCl_3$)δ:3.39 (3 H, s), 3.64 - 3.74 (2 H, m), 3.93 - 4.03 (4 H, m), 4.89 (2 H, s), 5.49 (1 H, s), 6.59 (1 H, d, J = 1.7 Hz), 6.74 (1 H, s), 7.08 - 7.18 (5 H, m), 7.32 (1 H, d, J = 8.3 Hz), 7.88 (1 H, s), 8.16 (1 H, s).

Example 282

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-amino-2-oxoethyl)amino]sulfonyl}carbamate

yield: 10%, LC-MS purity: 100%, m/z=555[M-H$^+$], retention time=1.63 min.

Example 283

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(cyclohexylmethyl)amino]sulfonyl}carbamate

yield: 50%, LC-MS purity: 100%, m/z=594[M-H$^+$], retention time=2.05 min.

Example 284

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(cycloheptylamino)sulfonyl]carbamate

yield: 37%, LC-MS purity: 100%, m/z=594[M-H$^+$], retention time=2.05 min.

Example 285

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(4-

methylcyclohexyl)amino]sulfonyl}carbamate
yield: 44%, LC-MS purity: 100%, m/z=594[M-H$^+$], retention time=2.06 min.

Example 286

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(3-isopropoxypropyl)amino]sulfonyl}carbamate
yield: 74%, LC-MS purity: 95%, m/z=598[M-H$^+$], retention time=2.00 min.

Example 287

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-phenylethyl)amino]sulfonyl}carbamate
yield: 61%, LC-MS purity: 100%, m/z=602[M-H$^+$], retention time=1.95 min.

Example 288

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate
yield: 58%, LC-MS purity: 100%, m/z=608[M-H$^+$], retention time=2.03 min.

Example 289

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-oxoazepan-3-yl)amino]sulfonyl}carbamate
yield: 51%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention time=1.80 min.

Example 290

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(2,3-dihydro-1H-inden-2-ylamino)sulfonyl]carbamate
yield: 63%, LC-MS purity: 100%, m/z=614[M-H$^+$], retention time=2.00 min.

Example 291

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(2,3-dihydro-1H-inden-1-

457

ylamino)sulfonyl]carbamate

yield: 55%, LC-MS purity: 100%, m/z=614[M-H$^+$], retention time=2.02 min.

Example 292

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(1,2,3,4-tetrahydronaphthalen-1-ylamino)sulfonyl]carbamate

yield: 56%, LC-MS purity: 100%, m/z=628[M-H$^+$], retention time=2.05 min.

Example 293

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-phenoxyethyl)amino]sulfonyl}carbamate

yield: 70%, LC-MS purity: 95%, m/z=618[M-H$^+$], retention time=1.94 min.

Example 294

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(4-methoxybenzyl)amino]sulfonyl}carbamate

yield: 66%, LC-MS purity: 95%, m/z=618[M-H$^+$], retention time=1.92 min.

Example 295

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[3-(2-oxopyrrolidin-1-yl)propyl]amino}sulfonyl)carbamate

yield: 41%, LC-MS purity: 100%, m/z=623[M-H$^+$], retention time=1.76 min.

Example 296

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (pyrrolidin-1-ylsulfonyl)carbamate

yield: 65%, LC-MS purity: 95%, m/z=552[M-H$^+$], retention time=1.95 min.

Example 297

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (piperidin-1-ylsulfonyl)carbamate

yield: 50%, LC-MS purity: 100%, m/z=566[M-H$^+$], retention time=1.99 min.

Example 298

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-methoxyethyl)(methyl)amino]sulfonyl}carbamate

yield: 58%, LC-MS purity: 100%, m/z=570[M-H$^+$], retention time=1.89 min.

Example 299

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(4-methylpiperidin-1-yl)sulfonyl]carbamate

yield: 46%, LC-MS purity: 100%, m/z=580[M-H$^+$], retention time=2.05 min.

Example 300

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(dipropylamino)sulfonyl]carbamate

yield: 57%, LC-MS purity: 100%, m/z=582[M-H$^+$], retention time=2.15 min.

Example 301

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[ethyl(2-methoxyethyl)amino]sulfonyl}carbamate

yield: 62%, LC-MS purity: 100%, m/z=584[M-H$^+$], retention time=1.97 min.

Example 302

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (thiomorpholin-4-ylsulfonyl)carbamate

yield: 49%, LC-MS purity: 97%, m/z=584[M-H$^+$], retention time=1.88 min.

Example 303

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[cyclohexyl(methyl)amino]sulfonyl}carbamate

yield: 61%, LC-MS purity: 100%, m/z=594[M-H$^+$], retention

time=2.15 min.

Example 304

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}carbamate

yield: 54%, LC-MS purity: 95%, m/z=596[M-H$^+$], retention time=1.95 min.

Example 305

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}carbamate

yield: 61%, LC-MS purity: 95%, m/z=596[M-H$^+$], retention time=1.95 min.

Example 306

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2R,6S)-2,6-dimethylmorpholin-4-yl]sulfonyl}carbamate

yield: 51%, LC-MS purity: 95%, m/z=596[M-H$^+$], retention time=1.85 min.

Example 307

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (1,3-dihydro-2H-isoindol-2-ylsulfonyl)carbamate

yield: 47%, LC-MS purity: 100%, m/z=600[M-H$^+$], retention time=1.97 min.

Example 308

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[benzyl(methyl)amino]sulfonyl}carbamate

yield: 51%, LC-MS purity: 100%, m/z=602[M-H$^+$], retention time=2.03 min.

Example 309

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[4-(aminocarbonyl)piperidin-1-yl]sulfonyl}carbamate

yield: 3%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention

time=1.70 min.

Example 310

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[3-(aminocarbonyl)piperidin-1-yl]sulfonyl}carbamate

yield: 30%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention time=1.70 min.

Example 311

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[3-(acetylamino)pyrrolidin-1-yl]sulfonyl}carbamate

yield: 37%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention time=1.70 min.

Example 312

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[2-(dimethylamino)ethyl]amino}sulfonyl)carbamate

yield: 33%, LC-MS purity: 100%, m/z=569[M-H$^+$], retention time=1.67 min.

Example 313

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(piperidin-1-ylamino)sulfonyl]carbamate

yield: 5%, LC-MS purity: 90%, m/z=581[M-H$^+$], retention time=1.65 min.

Example 314

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[3-(dimethylamino)propyl]amino}sulfonyl)carbamate

yield: 53%, LC-MS purity: 100%, m/z=583[M-H$^+$], retention time=1.67 min.

Example 315

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-pyrrolidin-1-ylethyl)amino]sulfonyl}carbamate

yield: 31%, LC-MS purity: 100%, m/z=595[M-H$^+$], retention

961

time=1.70 min.

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.89 - 2.00 (4 H, m), 3.07 (2 H, t, J = 7.0 Hz), 3.12 - 3.24 (4 H, m), 3.26 - 3.33 (2 H, t, J = 6.9 Hz), 3.44 (3 H, s), 3.72 - 3.75 (2 H, m), 4.09 - 4.12 (2 H, m), 4.92 (2 H, s), 6.68 (1 H, d, J = 2.5 Hz), 6.88 (1 H, dd, J = 8.6, 2.5 Hz), 7.48 (1 H, d, J = 8.6 Hz), 7.99 (1 H, d, J = 2.2 Hz), 8.22 (1 H, d, J = 1.2 Hz).

Example 316

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(pyridin-2-ylmethyl)amino]sulfonyl}carbamate

yield: 50%, LC-MS purity: 100%, m/z=589[M-H$^+$], retention time=1.77 min.

Example 317

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(pyridin-4-ylmethyl)amino]sulfonyl}carbamate

yield: 49%, LC-MS purity: 100%, m/z=589[M-H$^+$], retention time=1.72 min.

Example 318

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate

yield: 58%, LC-MS purity: 100%, m/z=603[M-H$^+$], retention time=1.80 min.

Example 319

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-pyridin-4-ylethyl)amino]sulfonyl}carbamate

yield: 67%, LC-MS purity: 100%, m/z=603[M-H$^+$], retention time=1.75 min.

Example 320

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-pyridin-3-ylethyl)amino]sulfonyl}carbamate

yield: 54%, LC-MS purity: 100%, m/z=603[M-H$^+$], retention time=1.77 min.

^{1}H-NMR (400 MHz, $CDCl_3$)δ:2.61 (2 H, d, J = 3.7 Hz), 3.00 - 3.09 (2 H, m), 3.39 (3 H, s), 3.62 - 3.69 (2 H, m), 3.93 - 4.00 (2 H, m), 4.89 (2 H, s), 5.45 - 5.57 (1 H, m), 6.58 (1 H, d, J = 2.2 Hz), 6.69 (1 H, d, J = 8.8 Hz), 7.02 (1 H, m), 7.33 (2 H, d, J = 8.8 Hz), 7.87 (1 H, d, J = 2.2 Hz), 8.14 (1 H, d, J = 1.0 Hz), 8.25 - 8.34 (2 H, m).

Example 321

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl ({[3-(1H-imidazol-1-yl)propyl]amino}sulfonyl)carbamate

yield: 41%, LC-MS purity: 100%, m/z=606[M-H$^+$], retention time=1.70 min.

Example 322

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-morpholin-4-ylethyl)amino]sulfonyl}carbamate

yield: 50%, LC-MS purity: 100%, m/z=611[M-H$^+$], retention time=1.72 min.

Example 323

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl {[(2-anilinoethyl)amino]sulfonyl}carbamate

yield: 49%, LC-MS purity: 100%, m/z=617[M-H$^+$], retention time=1.91 min.

Example 324

2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl [(4-methylpiperazin-1-yl)sulfonyl]carbamate

yield: 20%, LC-MS purity: 100%, m/z=581[M-H$^+$], retention time=1.67 min.

Example 325

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl

463

[(isopropylamino)sulfonyl]carbamate
yield: 51%, LC-MS purity: 100%, m/z=568[M-H$^+$], retention time=1.96 min.

Example 326

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-hydroxyethyl)amino]sulfonyl}carbamate
yield: 46%, LC-MS purity: 100%, m/z=570[M-H$^+$], retention time=1.76 min.

Example 327

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-cyanoethyl)amino]sulfonyl}carbamate
yield: 64%, LC-MS purity: 95%, m/z=579[M-H$^+$], retention time=1.79 min.

Example 328

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(tert-butylamino)sulfonyl]carbamate
yield: 52%, LC-MS purity: 100%, m/z=582[M-H$^+$], retention time=2.02 min.
^{1}H-NMR (400 MHz, $CDCl_3$)δ:1.30 (9 H, s), 1.86 - 1.94 (2 H, m), 2.52 (2 H, t, J = 7.5 Hz), 3.43 (3 H, s), 3.69 - 3.75 (2 H, m), 4.05 - 4.13 (4 H, m), 5.08 (1 H, s), 6.67 (1 H, d, J = 2.5 Hz), 6.81 (1 H, dd, J = 8.3, 2.5 Hz), 7.17 (1 H, d, J = 8.6 Hz), 7.99 (1 H, d, J = 2.2 Hz), 8.26 (1 H, s).

Example 329

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(3-hydroxypropyl)amino]sulfonyl}carbamate
yield: 47%, LC-MS purity: 100%, m/z=584[M-H$^+$], retention time=1.78 min.

Example 330

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-

methoxyethyl)amino]sulfonyl}carbamate

yield: 65%, LC-MS purity: 90%, m/z=584[M-H$^+$], retention time=1.85 min.

Example 331

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(cyclopentylamino)sulfonyl]carbamate

yield: 58%, LC-MS purity: 100%, m/z=594[M-H$^+$], retention time=2.02 min.

Example 332

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(1-ethylpropyl)amino]sulfonyl}carbamate

yield: 62%, LC-MS purity: 100%, m/z=596[M-H$^+$], retention time=2.08 min.

Example 333

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(3-methylbutyl)amino]sulfonyl}carbamate

yield: 59%, LC-MS purity: 100%, m/z=596[M-H$^+$], retention time=2.06 min.

Example 334

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(1,2-dimethylpropyl)amino]sulfonyl}carbamate

yield: 58%, LC-MS purity: 100%, m/z=596[M-H$^+$], retention time=2.07 min.

Example 335

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(1-methylbutyl)amino]sulfonyl}carbamate

yield: 59%, LC-MS purity: 100%, m/z=596[M-H$^+$], retention time=2.08 min.

Example 336

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-

(2-methoxyethoxy)phenyl]propyl {[(4-hydroxybutyl)amino]sulfonyl}carbamate
yield: 45%, LC-MS purity: 100%, m/z=598[M-H$^+$], retention time=1.80 min.

Example 337

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(cyclohexylamino)sulfonyl]carbamate
yield: 60%, LC-MS purity: 100%, m/z=608[M-H$^+$], retention time=2.07 min.

Example 338

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(tetrahydrofuran-2-ylmethyl)amino]sulfonyl}carbamate
yield: 66%, LC-MS purity: 100%, m/z=610[M-H$^+$], retention time=1.88 min.

Example 339

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(1,3-dimethylbutyl)amino]sulfonyl}carbamate
yield: 57%, LC-MS purity: 100%, m/z=610[M-H$^+$], retention time=2.13 min.

Example 340

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[2-(acetylamino)ethyl]amino}sulfonyl)carbamate
yield: 25%, LC-MS purity: 100%, m/z=611[M-H$^+$], retention time=1.74 min.

Example 341

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate
yield: 56%, LC-MS purity: 100%, m/z=612[M-H$^+$], retention time=1.94 min.

Example 342

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[1-(methoxymethyl)propyl]amino}sulfonyl)carbamate
yield: 54%, LC-MS purity: 95%, m/z=612[M-H$^+$], retention time=1.98 min.

Example 343

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(3-ethoxypropyl)amino]sulfonyl}carbamate
yield: 57%, LC-MS purity: 100%, m/z=612[M-H$^+$], retention time=1.94 min.

Example 344

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[3-(methylthio)propyl]amino}sulfonyl)carbamate
yield: 59%, LC-MS purity: 100%, m/z=614[M-H$^+$], retention time=1.96 min.

Example 345

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(benzylamino)sulfonyl]carbamate
yield: 57%, LC-MS purity: 100%, m/z=616[M-H$^+$], retention time=1.99 min.

Example 346

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-amino-2-oxoethyl)amino]sulfonyl}carbamate
yield: 16%, LC-MS purity: 100%, m/z=583[M-H$^+$], retention time=1.68 min.

Example 347

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(cyclohexylmethyl)amino]sulfonyl}carbamate
yield: 61%, LC-MS purity: 100%, m/z=622[M-H$^+$], retention time=2.13 min.

Example 348

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(cycloheptylamino)sulfonyl]carbamate

yield: 48%, LC-MS purity: 100%, m/z=622[M-H$^+$], retention time=2.13 min.

^{1}H-NMR (400 MHz, $CDCl_3$)δ:1.34 - 1.60 (10 H, m), 1.87 - 1.96 (4 H, m), 2.53 (2 H, t, J = 7.3 Hz), 3.43 (3 H, s), 3.38 - 3.46 (1 H, m), 3.70 - 3.75 (2 H, m), 4.05 - 4.14 (4 H, m), 5.00 - 5.09 (1 H,m), 6.68 (1 H, d, J = 2.2 Hz), 6.82 (1 H, dd, J = 8.6, 2.5 Hz), 7.18 (1 H, d, J = 8.6 Hz), 8.00 (1 H, d, J = 2.0 Hz), 8.26 (1 H, s).

Example 349

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(cycloheptylamino)sulfonyl]carbamate

yield: 58%, LC-MS purity: 100%, m/z=622[M-H$^+$], retention time=2.13 min.

Example 350

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(3-isopropoxypropyl)amino]sulfonyl}carbamate

yield: 53%, LC-MS purity: 100%, m/z=626[M-H$^+$], retention time=2.00 min.

Example 351

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenylethyl)amino]sulfonyl}carbamate

yield: 54%, LC-MS purity: 100%, m/z=630[M-H$^+$], retention time=2.03 min.

Example 352

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate

yield: 47%, LC-MS purity: 100%, m/z=636[M-H$^+$], retention

time=2.00 min.

Example 353

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-oxoazepan-3-yl)amino]sulfonyl}carbamate

yield: 48%, LC-MS purity: 90%, m/z=637[M-H$^+$], retention time=1.81 min.

Example 354

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(2,3-dihydro-1H-inden-2-ylamino)sulfonyl]carbamate

yield: 54%, LC-MS purity: 100%, m/z=642[M-H$^+$], retention time=2.04 min.

Example 355

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(2,3-dihydro-1H-inden-1-ylamino)sulfonyl]carbamate

yield: 51%, LC-MS purity: 100%, m/z=642[M-H$^+$], retention time=2.08 min.

Example 356

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(1,2,3,4-tetrahydronaphthalen-1-ylamino)sulfonyl]carbamate

yield: 51%, LC-MS purity: 100%, m/z=656[M-H$^+$], retention time=2.11 min.

Example 357

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenoxyethyl)amino]sulfonyl}carbamate

yield: 47%, LC-MS purity: 100%, m/z=646[M-H$^+$], retention time=2.00 min.

^{1}H-NMR (400 MHz, $CDCl_3$)δ:1.77 - 1.89 (2 H, m), 2.50 (2 H, t, J = 7.2 Hz), 3.42 (3 H, s), 3.38 - 3.47 (2 H, m), 3.65 - 3.73 (2 H, m), 3.98 - 4.08 (6 H, m), 5.53 - 5.65 (1 H, m), 6.66 (1 H, d, J = 2.5 Hz), 6.76 - 6.86 (3 H, m), 6.92 (1 H, t, J = 7.1

Hz), 7.13 (1 H, d, J = 8.6 Hz), 7.23 (2 H, t, J = 7.8 Hz), 7.98 (1 H, d, J = 2.0 Hz), 8.25 (1 H, s).

Example 358

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(4-methoxybenzyl)amino]sulfonyl}carbamate

yield: 48%, LC-MS purity: 100%, m/z=646[M-H$^+$], retention time=1.98 min.

Example 359

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[3-(2-oxopyrrolidin-1-yl)propyl]amino}sulfonyl)carbamate

yield: 40%, LC-MS purity: 82%, m/z=651[M-H$^+$], retention time=1.80 min.

Example 360

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (pyrrolidin-1-ylsulfonyl)carbamate

yield: 57%, LC-MS purity: 100%, m/z=580[M-H$^+$], retention time=2.00 min.

Example 361

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (piperidin-1-ylsulfonyl)carbamate

yield: 59%, LC-MS purity: 100%, m/z=594[M-H$^+$], retention time=2.05 min.

Example 362

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-methoxyethyl)(methyl)amino]sulfonyl}carbamate

yield: 59%, LC-MS purity: 100%, m/z=598[M-H$^+$], retention time=1.95 min.

Example 363

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(4-methylpiperidin-1-

yl)sulfonyl]carbamate

yield: 46%, LC-MS purity: 94%, m/z=608[M-H$^+$], retention time=2.11 min.

Example 364

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(dipropylamino)sulfonyl]carbamate

yield: 50%, LC-MS purity: 100%, m/z=610[M-H$^+$], retention time=2.19 min.

Example 365

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[ethyl(2-methoxyethyl)amino]sulfonyl}carbamate

yield: 50%, LC-MS purity: 100%, m/z=612[M-H$^+$], retention time=2.02 min.

Example 366

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (thiomorpholin-4-ylsulfonyl)carbamate

yield: 59%, LC-MS purity: 100%, m/z=612[M-H$^+$], retention time=1.94 min.

Example 367

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[cyclohexyl(methyl)amino]sulfonyl}carbamate

yield: 60%, LC-MS purity: 100%, m/z=622[M-H$^+$], retention time=2.19 min.

Example 368

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}carbamate

yield: 52%, LC-MS purity: 100%, m/z=624[M-H$^+$], retention time=2.01 min.

Example 369

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-

(2-methoxyethoxy)phenyl]propyl {[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}carbamate
yield: 59%, LC-MS purity: 100%, m/z=624[M-H$^+$], retention time=2.01 min.

Example 370

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2R,6S)-2,6-dimethylmorpholin-4-yl]sulfonyl}carbamate
yield: 55%, LC-MS purity: 100%, m/z=624[M-H$^+$], retention time=1.92 min.

Example 371

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (1,3-dihydro-2H-isoindol-2-ylsulfonyl)carbamate
yield: 56%, LC-MS purity: 100%, m/z=628[M-H$^+$], retention time=2.04 min.

Example 372

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[benzyl(methyl)amino]sulfonyl}carbamate
yield: 57%, LC-MS purity: 100%, m/z=630[M-H$^+$], retention time=2.10 min.

Example 373

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[4-(aminocarbonyl)piperidin-1-yl]sulfonyl}carbamate
yield: 6%, LC-MS purity: 100%, m/z=637[M-H$^+$], retention time=1.76 min.

Example 374

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[3-(aminocarbonyl)piperidin-1-yl]sulfonyl}carbamate
yield: 47%, LC-MS purity: 100%, m/z=637[M-H$^+$], retention time=1.77 min.

Example 375

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[3-(acetylamino)pyrrolidin-1-yl]sulfonyl}carbamate

yield: 48%, LC-MS purity: 100%, m/z=637[M-H$^+$], retention time=1.77 min.

Example 376

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[2-(dimethylamino)ethyl]amino}sulfonyl)carbamate

yield: 49%, LC-MS purity: 100%, m/z=597[M-H$^+$], retention time=1.72 min.

Example 377

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[3-(dimethylamino)propyl]amino}sulfonyl)carbamate

yield: 39%, LC-MS purity: 100%, m/z=611[M-H$^+$], retention time=1.72 min.

Example 378

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyrrolidin-1-ylethyl)amino]sulfonyl}carbamate

yield: 48%, LC-MS purity: 100%, m/z=623[M-H$^+$], retention time=1.74 min.

Example 379

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(pyridin-2-ylmethyl)amino]sulfonyl}carbamate

yield: 43%, LC-MS purity: 100%, m/z=617[M-H$^+$], retention time=1.83 min.

Example 380

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(pyridin-4-ylmethyl)amino]sulfonyl}carbamate

yield: 48%, LC-MS purity: 100%, m/z=617[M-H$^+$], retention time=1.78 min.

Example 381

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate

yield: 49%, LC-MS purity: 100%, m/z=631[M-H$^+$], retention time=1.87 min.

Example 382

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-4-ylethyl)amino]sulfonyl}carbamate

yield: 48%, LC-MS purity: 100%, m/z=631[M-H$^+$], retention time=1.81 min.

Example 383

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-3-ylethyl)amino]sulfonyl}carbamate

yield: 43%, LC-MS purity: 100%, m/z=631[M-H$^+$], retention time=1.83 min.

Example 384

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl ({[3-(1H-imidazol-1-yl)propyl]amino}sulfonyl)carbamate

yield: 39%, LC-MS purity: 100%, m/z=634[M-H$^+$], retention time=1.76 min.

Example 385

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-morpholin-4-ylethyl)amino]sulfonyl}carbamate

yield: 46%, LC-MS purity: 100%, m/z=639[M-H$^+$], retention time=1.77 min.

Example 386

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-anilinoethyl)amino]sulfonyl}carbamate

yield: 47%, LC-MS purity: 89%, m/z=645[M-H$^+$], retention

time=1.97 min.

Example 387

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl [(4-methylpiperazin-1-yl)sulfonyl]carbamate

yield: 36%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention time=1.72 min.

Example 388

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl [(pentylamino)sulfonyl]carbamate

yield: 21%, LC-MS purity: 100%, m/z=499[M-H$^+$], retention time=2.11 min.

Example 389

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

yield: 13%, LC-MS purity: 100%, m/z=515[M-H$^+$], retention time=2.06 min.

Example 390

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenylethyl)amino]sulfonyl}carbamate

yield: 16%, LC-MS purity: 100%, m/z=533[M-H$^+$], retention time=2.14 min.

Example 391

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate

yield: 12%, LC-MS purity: 100%, m/z=539[M-H$^+$], retention time=2.13 min.

Example 392

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenoxyethyl)amino]sulfonyl}carbamate

yield: 19%, LC-MS purity: 87%, m/z=549[M-H$^+$], retention time=2.09 min.

Example 393

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl ({[2-(2-methoxyphenyl)ethyl]amino}sulfonyl)carbamate

yield: 18%, LC-MS purity: 100%, m/z=563[M-H$^+$], retention time=2.10 min.

Example 394

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2,2-diphenylethyl)amino]sulfonyl}carbamate

yield: 23%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention time=2.26 min.

Example 395

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(1,2-diphenylethyl)amino]sulfonyl}carbamate

yield: 30%, LC-MS purity: 100%, m/z=609[M-H$^+$], retention time=2.23 min.

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.30 - 1.42 (2 H, m), 1.45 - 1.68 (4 H, m), 1.69 - 1.79 (4 H, m), 1.88 - 1.97 (2 H, m), 2.45 - 2.52 (2 H, m), 3.01 - 3.09 (1 H, m), 3.12 - 3.18 (1 H, m), 3.44 (3 H, s), 3.71 - 3.76 (2 H, m), 3.79 - 3.84 (1 H, m), 3.86 - 3.91 (1 H, m), 4.05 - 4.11 (2 H, m), 4.18 - 4.25 (1 H, m), 4.59 - 4.67 (1 H, m), 5.59 - 5.67 (1 H, m), 6.34 - 6.40 (1 H, m), 6.50 (3 H, d, J = 2.2 Hz), 6.92 (1 H, d, J = 8.3 Hz), 6.97 - 7.08 (3 H, m), 7.14 - 7.24 (7 H, m).

Example 396

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(pyridin-2-ylmethyl)amino]sulfonyl}carbamate

yield: 23%, LC-MS purity: 81%, m/z=520[M-H$^+$], retention time=2.03 min.

Example 397

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate

yield: 27%, LC-MS purity: 100%, m/z=534[M-H$^+$], retention time=2.04 min.

Example 398

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl ({[(5-methylpyrazin-2-yl)methyl]amino}sulfonyl)carbamate

yield: 28%, LC-MS purity: 100%, m/z=535[M-H$^+$], retention time=1.99 min.

Example 399

3-[2-(cyclohexyloxy)-4-(2-methoxyethoxy)phenyl]propyl {[(3-methoxypropyl)amino]sulfonyl}carbamate

yield: 20%, LC-MS purity: 100%, m/z=501[M-H$^+$], retention time=2.08 min.

Example 400

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl [(pentylamino)sulfonyl]carbamate

yield: 57%, LC-MS purity: 88%, m/z=471[M-H$^+$], retention time=2.05 min.

Example 401

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

yield: 37%, LC-MS purity: 100%, m/z=487[M-H$^+$], retention time=2.04 min.

Example 402

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenylethyl)amino]sulfonyl}carbamate

yield: 36%, LC-MS purity: 100%, m/z=505[M-H$^+$], retention time=2.05 min.

Example 403

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate

yield: 50%, LC-MS purity: 100%, m/z=511[M-H$^+$], retention time=2.07 min.

Example 404

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-phenoxyethyl)amino]sulfonyl}carbamate

yield: 48%, LC-MS purity: 89%, m/z=521[M-H$^+$], retention time=2.04 min.

Example 405

477

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl ({[2-(2-methoxyphenyl)ethyl]amino}sulfonyl)carbamate
yield: 46%, LC-MS purity: 100%, m/z=535[M-H$^+$], retention time=2.06 min.

Example 406

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2,2-diphenylethyl)amino]sulfonyl}carbamate
yield: 70%, LC-MS purity: 100%, m/z=581[M-H$^+$], retention time=2.12 min.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.23 - 0.31 (2 H, m), 0.49 - 0.58 (2 H, m), 1.17 - 1.28 (1 H, m), 1.78 - 1.90 (2 H, m), 2.59 (2 H, t, J = 7.3 Hz), 3.43 (3 H, s), 3.63 (2 H, d, J = 7.8 Hz), 3.69 - 3.76 (4 H, m), 3.97 - 4.07 (4 H, m), 4.20 (1 H, t, J = 7.8 Hz), 5.03 (1 H, s), 6.36 (1 H, d, J = 8.3 Hz), 6.44 (1 H, d, J = 1.7 Hz), 6.94 (1 H, d, J = 8.1 Hz), 7.11 - 7.25 (1 H, m).

Example 407

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(1,2-diphenylethyl)amino]sulfonyl}carbamate
yield: 44%, LC-MS purity: 100%, m/z=581[M-H$^+$], retention time=2.12 min.

Example 408

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(pyridin-2-ylmethyl)amino]sulfonyl}carbamate
yield: 37%, LC-MS purity: 100%, m/z=492[M-H$^+$], retention time=1.97 min.

Example 409

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate
yield: 52%, LC-MS purity: 100%, m/z=506[M-H$^+$], retention time=2.01 min.

Example 410

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl ({[(5-methylpyrazin-2-yl)methyl]amino}sulfonyl)carbamate

yield: 68%, LC-MS purity: 100%, m/z=507[M-H$^+$], retention time=1.93 min.

Example 411

3-[2-(cyclopropylmethoxy)-4-(2-methoxyethoxy)phenyl]propyl {[(3-methoxypropyl)amino]sulfonyl}carbamate

yield: 43%, LC-MS purity: 100%, m/z=473[M-H$^+$], retention time=2.01 min.

Example 412

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl [(pentylamino)sulfonyl]carbamate

yield: 51%, LC-MS purity: 81%, m/z=501[M-H$^+$], retention time=2.08 min.

Example 413

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

yield: 36%, LC-MS purity: 100%, m/z=517[M-H$^+$], retention time=2.01 min.

Example 414

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(2-phenylethyl)amino]sulfonyl}carbamate

yield: 45%, LC-MS purity: 100%, m/z=535[M-H$^+$], retention time=2.01 min.

Example 415

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl ({[2-(2-thienyl)ethyl]amino}sulfonyl)carbamate

yield: 46%, LC-MS purity: 100%, m/z=541[M-H$^+$], retention time=1.99 min.

Example 416

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(2-phenoxyethyl)amino]sulfonyl}carbamate

yield: 54%, LC-MS purity: 89%, m/z=551[M-H$^+$], retention time=2.02 min.

Example 417

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl ({[2-(2-methoxyphenyl)ethyl]amino}sulfonyl)carbamate

yield: 49%, LC-MS purity: 100%, m/z=565[M-H$^+$], retention time=2.03 min.

Example 418

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(2,2-diphenylethyl)amino]sulfonyl}carbamate

yield: 41%, LC-MS purity: 100%, m/z=611[M-H$^+$], retention time=2.07 min.

Example 419

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(1,2-diphenylethyl)amino]sulfonyl}carbamate

yield: 41%, LC-MS purity: 100%, m/z=611[M-H$^+$], retention time=2.09 min.

Example 420

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(pyridin-2-ylmethyl)amino]sulfonyl}carbamate

yield: 17%, LC-MS purity: 88%, m/z=522[M-H$^+$], retention time=1.96 min.

Example 421

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate

yield: 17%, LC-MS purity: 100%, m/z=536[M-H$^+$], retention

time=1.98 min.

Example 422

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl ({[(5-methylpyrazin-2-yl)methyl]amino}sulfonyl)carbamate

yield: 18%, LC-MS purity: 100%, m/z=537[M-H$^+$], retention time=1.86 min.

Example 423

3-[4-(2-methoxyethoxy)-2-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(3-methoxypropyl)amino]sulfonyl}carbamate

yield: 21%, LC-MS purity: 100%, m/z=503[M-H$^+$], retention time=1.95 min.

Example 424

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}acrylic acid (1.73 g) in acetonitrile (30 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.49 g), 4-dimethylaminopyridine (0.95 g) and pentane-1-sulfonamide (592 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:19 - 45:55, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (952 mg, yield: 42%) as white crystals. melting point 104.6-106.5°C.

Example 425

To a solution of ethyl 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-

2-yl)ethoxy]phenyl}propanoate (0.77 g) in tetrahydrofuran (4 ml) and ethanol (4 ml) was added a 1N aqueous sodium hydroxide solution (4 ml), and the mixture was stirred at 50°C for 30 min. After allowing to cool to room temperature, 1N hydrochloric acid (4 ml) was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtrated and concentrated to give a yellow oil.

To a solution of the obtained oil in acetonitrile (10 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (588 mg), 4-dimethylaminopyridine (283 mg) and pentane-1-sulfonamide (233 mg), and the mixture was stirred overnight at room temperature. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution, and saturated brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:9 - 55:45, v/v) to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}-N-(pentylsulfonyl)propanamide (361 mg, yield: 40%) as white crystals. melting point 96.5-97.5°C.

Example 426

To a solution of 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propan-1-ol (274 mg) in toluene (8 ml) under ice-cooling chlorosulfonylisocyanate (109 mg) was added, and the mixture was stirred for 30 min. Pyridine (175 mg) was added to the reaction mixture and the mixture was stirred for 1 hr. A 28% ammonia solution (268 mg) was added, and the mixture was stirred at room temperature for 1.5 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained

residue was subjected to silica gel column chromatography, and eluted with ethyl acetate to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propyl (aminosulfonyl)carbamate (210 mg, yield: 58%) as colorless crystals. melting point 153.2-153.8°C.

Example 427

To a solution of 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propan-1-ol (404 mg) in toluene (10 ml) was added chlorosulfonylisocyanate (161 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (258 mg) was added to the reaction mixture and the mixture was stirred for 1 hr. 2-(2-Aminoethyl)-pyridine (796 mg) was added, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1 - 7:3, v/v) to give 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (328 g, yield: 50%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.82 - 1.95 (2 H, m), 2.54 (2 H, t, J = 7.4 Hz), 3.06 (2 H, t, J = 6.3 Hz), 3.43 (3 H, s), 3.48 - 3.54 (2 H, m), 3.72 (2 H, dd, J = 5.5, 4.0 Hz), 4.03 - 4.14 (4 H, m), 6.60 - 6.66 (1 H, m), 6.76 (1 H, dd, J = 8.5, 2.6 Hz), 7.10 - 7.19 (3 H, m), 7.57 - 7.65 (1 H, m), 7.76 - 7.80 (1 H, m), 7.95 (1 H, d, J = 2.4 Hz), 8.47 - 8.52 (1 H, m).

Example 428

To a solution of 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propan-1-ol (406 mg) in toluene (10 ml) was added chlorosulfonylisocyanate (162 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (259 mg) was added to the reaction mixture and the mixture was

stirred for 1 hr. 3-Methoxypropylamine (584 mg) was added, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3 - 3:2, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propyl {[(3-methoxypropyl)amino]sulfonyl}carbamate (435 mg, yield: 70%) as colorless crystals. melting point 87.9-89.0°C.

Example 429

To a solution of 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propan-1-ol (400 mg) in toluene (10 ml) was added chlorosulfonylisocyanate (160 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (255 mg) was added to the reaction mixture and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (665 mg) was added, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 1:1, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (256 mg, yield: 41%) as colorless crystals. melting point 87.5-88.4°C.

Example 430

To a solution of 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}propan-1-ol (500 mg) in toluene (13 ml) was added chlorosulfonylisocyanate (155 mg) under ice-

cooling, and the mixture was stirred for 30 min. Pyridine (248 mg) was added to the reaction mixture and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (648 mg) was added, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to HPLC (acetonitrile:water, containing 0.01% TFA, 5:95 - 100:0, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (145 mg, yield: 20%) as colorless crystals. melting point 68.0-69.2°C.

Example 431

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.60 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.14 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.44 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (0.77 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 8:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.35 g, yield: 38%) as colorless crystals. melting point 127-128°C.

Example 432

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.60 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.14 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.44 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 3-Methoxypropylamine (0.66 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 8:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl {[(3-methoxypropyl)amino]sulfonyl}carbamate (0.42 g, yield: 47%) as colorless crystals. melting point 98-100°C.

Example 433

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.60 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.14 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.44 ml) was added to the reaction mixture and the mixture was stirred for 1 hr. 1-Pentylamine (0.65 g) was added and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl [(pentylamino)sulfonyl]carbamate (0.23 g, yield: 26%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.81 - 0.94 (3 H, m), 1.19 - 1.39 (4 H, m), 1.45 - 1.73 (2 H, m), 2.97 - 3.12 (2 H, m), 3.44 (3 H, s), 3.74 (2 H, dd, J = 5.5, 4.0 Hz), 4.02 - 4.18 (2 H, m), 4.72 (2 H, dd, J = 6.6, 1.1 Hz), 4.91 - 5.05 (1 H, m), 6.09 - 6.26 (1 H, m), 6.58 - 6.71 (2 H, m), 6.83 - 6.94 (1 H, m), 7.13 (1 H, br.s.), 7.48 - 7.56 (1 H, m), 8.01 (1 H, d, J = 1.7 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Example 434

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.60 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.14 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.44 ml) was added to the reaction mixture, the mixture was stirred for 1 hr, 1-(2-aminoethyl)pyrrolidine (0.85 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with methanol-ethyl acetate (0:1 - 8:2, v/v), concentrated and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl {[(2-pyrrolidin-1-ylethyl)amino]sulfonyl}carbamate (0.40 g, yield: 43%) as colorless crystals. melting point 154-156°C.

Example 435

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.60 g) in acetonitrile

(5 ml) was added chlorosulfonylisocyanate (0.14 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.44 ml) was added to the reaction mixture, the mixture was stirred for 1 hr, phenethylamine (0.90 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 6:4, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl {[(2-phenylethyl)amino]sulfonyl}carbamate (0.49 g, yield: 53%) as colorless crystals. melting point 113-114°C.

Example 436

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.60 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.14 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.44 ml) was added to the reaction mixture, the mixture was stirred for 1 hr, 2-(2-aminoethyl)pyridine (1.46 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:8 - 9:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (0.43 g, yield: 46%) as

colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.05 (2 H, J = 6.2 Hz), 3.44 (3 H, s), 3.53 (2 H, t, J = 6.2 Hz), 3.74 (2 H, dd, J = 5.4, 3.9 Hz), 4.05 - 4.15 (2 H, m), 4.67 (2 H, dd, J = 6.4, 0.9 Hz), 6.06 - 6.23 (1 H, m), 6.57 - 6.70 (2 H, m), 6.86 (1 H, dd, J = 8.7, 2.4 Hz), 7.08 - 7.18 (2 H, m), 7.49 (1 H, d, J = 8.9 Hz), 7.54 - 7.66 (1 H, m), 8.00 (1 H, d, J = 2.1 Hz), 8.23 (1 H, d, J = 0.9 Hz), 8.44 - 8.54 (1 H, m).

Example 437

To a solution of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-ol (0.50 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.11 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.37 ml) was added to the reaction mixture, the mixture was stirred for 1 hr, pyrrolidine (0.44 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 6:4, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]prop-2-en-1-yl (pyrrolidin-1-ylsulfonyl)carbamate (0.53 g, yield: 73%) as colorless crystals. melting point 123-124°C.

Example 438

To a solution of 3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propan-1-ol (1.00 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.15 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.47 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether

(0.82 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 1:1, v/v) to give 3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.88 g, yield: 66%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.04 (9 H, s), 1.13 (6 H, d, J = 6.2 Hz), 1.85 - 2.01 (2 H, m), 2.54 (2 H, t, J = 7.4 Hz), 3.16 - 3.29 (2 H, m), 3.44 - 3.63 (3 H, m), 3.89 - 4.20 (6 H, m), 5.39 (1 H, t, J = 5.7 Hz), 6.63 (1 H, d, J = 2.4 Hz), 6.77 (1 H, dd, J = 8.5, 2.6 Hz), 7.17 (1 H, d, J = 8.5 Hz), 7.31 - 7.48 (7 H, m), 7.62 - 7.74 (7 H, m), 8.01 (1 H, d, J = 1.7 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Example 439

To a solution of 3-(4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.88 g) in tetrahydrofuran (5 ml) were added a tetra-n-butylammonium fluoride 1.0M-tetrahydrofuran solution (5.3 ml), and the mixture was stirred at room temperature for 6 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to HPLC (acetonitrile:water, containing 0.01% TFA, 5:95 - 100:0, v/v) to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.32 g, yield: 51%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.2 Hz), 1.88 - 2.00 (2 H, m), 2.01 - 2.13 (1 H, m), 2.58 (2 H, t, J = 7.3 Hz), 3.23 (2 H, q, J = 5.5 Hz), 3.47 - 3.65 (3 H, m), 3.95 (2 H, d, J = 4.1 Hz), 4.03 - 4.19 (4 H, m), 5.39 (1 H, t, J = 5.8 Hz), 6.69 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.5, 2.4 Hz), 7.20 (1 H, d, J = 8.5 Hz), 7.54 (1 H, br.s.), 8.02 (1 H, d, J = 2.3 Hz), 8.25 - 8.31 (1 H, m).

Example 440

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propan-1-ol (0.40 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.09 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 3-Methoxypropylamine (0.48 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 4:6, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propyl {[(3-methoxypropyl)amino]sulfonyl}carbamate (0.44 g, yield: 74%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.33 (6 H, d, J = 6.0 Hz), 1.75 - 2.02 (4 H, m), 2.55 (2 H, t, J = 7.5 Hz), 3.12 - 3.23 (2 H, m), 3.32 (3 H, s), 3.44 - 3.51 (2 H, t, J = 5.6 Hz), 4.15 (2 H, t, J = 6.4 Hz), 4.43 - 4.54 (1 H, m), 5.57 - 5.66 (1 H, m), 6.62 (1 H, d, J = 2.4 Hz), 6.77 (1 H, dd, J = 8.5, 2.6 Hz), 7.17 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.28 (1 H, d, J = 1.3 Hz).

Example 441

To a solution of 3-(2-{[3-chloro-5-

(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propan-1-ol (0.40 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.09 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (0.56 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.32 g, yield: 51%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.2 Hz), 1.32 (6 H, d, J = 6.0 Hz), 1.86 - 2.02 (2 H, m), 2.54 (2 H, t, J = 7.3 Hz), 3.23 (2 H, q, J = 5.5 Hz), 3.43 - 3.65 (3 H, m), 4.15 (2 H, t, J = 6.4 Hz), 4.39 - 4.57 (1 H, m), 5.37 (1 H, t, J = 5.7 Hz), 6.62 (1 H, d, J = 2.6 Hz), 6.77 (1 H, dd, J = 8.4, 2.5 Hz), 7.17 (1 H, d, J = 8.5 Hz), 7.37 (1 H, br.s.), 8.00 (1 H, d, J = 2.3 Hz), 8.28 (1 H, d, J = 1.1 Hz).

Example 442

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propan-1-ol (0.40 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.09 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Phenoxyethylamine (0.74 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 3:7, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propyl {[(2-phenoxyethyl)amino]sulfonyl}carbamate (0.30 g, yield: 46%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.0 Hz), 1.79 - 1.98 (2 H, m), 2.53 (2 H, t, J = 7.3 Hz), 3.41 - 3.56 (2 H, m), 4.01 - 4.15 (4 H, m), 4.39 - 4.57 (1 H, m), 5.45 - 5.56 (1 H, m), 6.62 (1 H, d, J = 2.6 Hz), 6.76 (1 H, dd, J = 8.5, 2.4 Hz), 6.82 - 6.90 (2 H, m), 6.92 - 7.01 (1 H, m), 7.14 (1 H, d, J = 8.5 Hz), 7.23 - 7.31 (2 H, m), 7.40 (1 H, br.s.), 8.00 (1 H, d, J = 1.9 Hz), 8.28 (1 H, dd, J = 2.1, 0.9 Hz).

Example 443

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propan-1-ol (0.40 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.09 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. N-(2-Methoxyethyl)methylamine (0.48 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 8:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propyl {[(2-methoxyethyl)(methyl)amino]sulfonyl}carbamate (0.42 g, yield: 70%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.0 Hz), 1.86 - 2.01

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(2 H, m), 2.54 (2 H, t, J = 7.4 Hz), 3.00 (3 H, s), 3.36 (3 H, s), 3.44 - 3.61 (4 H, m), 4.12 (2 H, t, J = 6.5 Hz), 4.40 - 4.57 (1 H, m), 6.62 (1 H, d, J = 2.4 Hz), 6.77 (1 H, dd, J = 8.5, 2.4 Hz), 7.17 (1 H, d, J = 8.5 Hz), 7.48 (1 H, br.s.), 8.00 (1 H, d, J = 1.9 Hz), 8.28 (1 H, dd, J = 2.1, 0.9 Hz).

Example 444

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propan-1-ol (0.40 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.09 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.30 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-(2-Aminoethyl)pyridine (0.66 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (0:1 - 8:2, v/v) to give 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (0.33 g, yield: 52%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.31 (6 H, d, J = 6.0 Hz), 1.74 - 1.94 (2 H, m), 2.46 (2 H, t, J = 7.4 Hz), 3.03 (2 H, t, J = 6.6 Hz), 3.47 (2 H, t, J = 6.5 Hz), 4.04 (2 H, t, J = 6.3 Hz), 4.36 - 4.57 (1 H, m), 6.60 (1 H, d, J = 2.4 Hz), 6.72 (1 H, dd, J = 8.5, 2.4 Hz), 7.02 - 7.20 (3 H, m), 7.58 (1 H, td, J = 7.7, 1.6 Hz), 7.96 (1 H, d, J = 2.1 Hz), 8.24 (1 H, d, J = 1.1 Hz), 8.47 (1 H, d, J = 4.3 Hz).

Example 445

To a solution of 2-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]ethanol (0.30 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.07 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine

(0.23 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (0.42 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 8:2, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]ethyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.26 g, yield: 56%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.13 (6 H, d, J = 6.2 Hz), 2.86 (2 H, t, J = 6.8 Hz), 3.16 (2 H, q, J = 5.7 Hz), 3.43 (3 H, s), 3.46 - 3.64 (3 H, m), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.03 - 4.14 (2 H, m), 4.34 (2 H, t, J = 6.9 Hz), 5.38 (1 H, t, J = 5.8 Hz), 6.66 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.5, 2.6 Hz), 7.23 (1 H, d, J = 8.7 Hz), 7.39 (1 H, br. s.), 8.02 (1 H, d, J = 2.1 Hz), 8.25 - 8.33 (1 H, m).

Example 446

To a solution of 2-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]ethanol (0.30 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.07 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.23 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminopropyl)isopropyl ether (0.48 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 8:2, v/v), concentrated, and

crystallized from ethyl acetate-hexane to give 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]ethyl {[(3-isopropoxypropyl)amino]sulfonyl}carbamate (0.31 g, yield: 66%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.13 (6 H, d, J = 6.2 Hz), 2.86 (2 H, t, J = 6.8 Hz), 3.16 (2 H, q, J = 5.7 Hz), 3.43 (3 H, s), 3.46 - 3.64 (3 H, m), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.03 - 4.14 (2 H, m), 4.34 (2 H, t, J = 6.9 Hz), 5.38 (1 H, t, J = 5.8 Hz), 6.66 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.5, 2.6 Hz), 7.23 (1 H, d, J = 8.7 Hz), 7.39 (1 H, br.s.), 8.02 (1 H, d, J = 2.1 Hz), 8.25 - 8.33 (1 H, m).

Example 447

To a solution of 2-[2-(benzyloxy)-4-(2-methoxyethoxy)phenyl]ethanol (0.30 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.07 ml) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.23 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 3-Methoxypropylamine (0.36 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 9:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]ethyl {[(3-methoxypropyl)amino]sulfonyl}carbamate (0.27 g, yield: 60%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.70 - 1.83 (2 H, m), 2.87 (2 H, t, J = 6.8 Hz), 3.09 (2 H, q, J = 6.2 Hz), 3.31 (3 H, s), 3.38 - 3.49 (5 H, m), 3.73 (2 H, dd, J = 5.6, 3.9 Hz), 4.08 (2 H, dd, J = 5.5, 4.0 Hz), 4.35 (2 H, t, J = 6.9 Hz), 5.52 - 5.64 (1 H,

m), 6.65 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.20 - 7.25 (1 H, m), 8.02 (1 H, d, J = 2.1 Hz), 8.30 (1 H, d, J = 1.1 Hz).

Example 448

To a solution of 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]ethanol (1.32 g) in acetonitrile (30 ml) was added chlorosulfonylisocyanate (0.54 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (1.62 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (1.98 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 1:1, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]ethyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.29 g, yield: 14%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.13 (6 H, d, J = 6.2 Hz), 2.86 (2 H, t, J = 6.8 Hz), 3.18 (2 H, q, J = 5.7 Hz), 3.42 - 3.63 (6 H, m), 4.35 (2 H, t, J = 6.9 Hz), 5.15 (2 H, s), 5.40 (1 H, t, J = 6.0 Hz), 6.80 (1 H, d, J = 2.4 Hz), 6.95 (1 H, dd, J = 8.5, 2.4 Hz), 7.24 (1 H, d, J = 8.5 Hz), 7.37 (1 H, s), 8.01 (1 H, d, J = 1.9 Hz), 8.29 (1 H, dd, J = 2.2, 1.0 Hz).

Example 449

To a solution of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (463 mg) in tetrahydrofuran (4 ml) and methanol (4 ml) was added platinum (IV) oxide (18 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hr. The

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reaction mixture was filtrated and the filtrate was concentrated to give a white solid. Recrystallization from ethyl acetate-hexane gave 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}-N-(pentylsulfonyl)propanamide (395.5 mg, yield: 85%) as white crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.43 - 0.54 (2 H, m), 0.55 - 0.63 (2 H, m), 0.90 (3 H, t, J = 7.0 Hz), 1.14 - 1.43 (4 H, m), 1.59 - 1.72 (2 H, m), 2.55 (2 H, t, J = 7.2 Hz), 2.95 (2 H, t, J = 7.2 Hz), 3.10 - 3.21 (2 H, m), 3.36 (1 H, tt, J = 6.1, 3.0 Hz), 3.71 - 3.83 (2 H, m), 3.91 - 4.08 (2 H, m), 6.51 (1 H, d, J = 2.7 Hz), 6.77 (1 H, dd, J = 8.3, 2.7 Hz), 7.18 (1 H, d, J = 8.7 Hz), 8.08 (1 H, d, J = 2.3 Hz), 8.37 (1 H, dd, J = 2.1, 0.9 Hz).

Example 450

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propan-1-ol (5.2 g) in acetonitrile (100 ml) was added chlorosulfonylisocyanate (2.1 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (4.1 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (6.8 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 6:4, v/v), concentrated, and crystallized from ethyl acetate-hexane to give, 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (5.2 g, yield: 65%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.0 Hz), 1.88 - 2.01

(2 H, m), 2.56 (2 H, t, J = 7.4 Hz), 3.23 (2 H, q, J = 5.7 Hz), 3.48 (3 H, s), 3.49 - 3.62 (3 H, m), 4.15 (2 H, t, J = 6.4 Hz), 5.15 (2 H, s), 5.39 (1 H, t, J = 5.9 Hz), 6.82 (1 H, d, J = 2.7 Hz), 6.94 (1 H, dd, J = 8.3, 2.7 Hz), 7.20 (1 H, d, J = 8.3 Hz), 7.42 (1 H, br. s.), 8.01 (1 H, d, J = 2.3 Hz), 8.27 (1 H, s).

Example 451

A mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.21 g), 4-dimethylaminopyridine (892 mg), and acetonitrile (10 ml) was stirred at room temperature for 10 min. To the mixture were added (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]acrylic acid (2.08 g) and pentane-1-sulfonamide (749 mg), and the mixture was stirred at room temperature for 15 hr. A 1M hydrochloric acid solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]-N-(pentylsulfonyl)acrylamide (708 mg, yield: 26%) as colorless crystals. melting point 165-166°C.

Example 452

A mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (150 mg), 4-dimethylaminopyridine (110 mg), and acetonitrile (3 ml) was stirred at room temperature for 10 min. To the mixture were added (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-oxopropoxy)phenyl]acrylic acid (250 mg) and pentane-1-sulfonamide (93 mg), and the mixture was stirred at room temperature for 15 hr. A 1M hydrochloric acid solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated.

The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-oxopropoxy)phenyl]-N-(pentylsulfonyl)acrylamide (70 mg, yield: 30%) as colorless crystals. melting point 187-188°C.

Example 453

A mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (940 mg), 4-dimethylaminopyridine (691 mg), and acetonitrile (5 ml) was stirred at room temperature for 10 min. To the mixture were added (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}acrylic acid (1.79 g) and pentane-1-sulfonamide (580 mg), and the mixture was stirred at room temperature for 15 hr. A 1M hydrochloric acid solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (1.19 g, yield: 52%) as colorless crystals. melting point 90-92°C.

Example 454

A mixture of (2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide (750 mg), 1M hydrochloric acid solution (5 ml), and tetrahydrofuran (15 ml) was stirred at 60°C for 1 hr. After cooling to room temperature, the mixture was concentrated. Water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained solid was recrystallized from ethyl acetate to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-

oxobutoxy)phenyl]-N-(pentylsulfonyl)acrylamide (418 mg, yield: 60%) as colorless crystals. melting point 180-181°C.

Example 455

A mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (247 mg), 4-dimethylaminopyridine (182 mg), and acetonitrile (5 ml) was stirred at room temperature for 10 min. To the mixture were added (2E)-3-(4-[2-(acetyloxy)-3-isopropoxypropoxy]-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylic acid (513 mg) and pentane-1-sulfonamide (152 mg), and the mixture was stirred at room temperature for 2.5 hr. A 1M hydrochloric acid solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:5 - 1:2, v/v). The obtained solid was recrystallized from diethyl ether-hexane to give 2-(3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)-1-(isopropoxymethyl)ethyl acetate (487 mg, yield: 76%) as colorless crystals. melting point 101-103°C.

Example 456

To a mixture of 2-(3-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)-1-(isopropoxymethyl)ethyl acetate (380 mg), tetrahydrofuran (6 ml), and ethanol (4 ml) was added a 1M sodium hydroxide solution (4 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water, and the mixture was neutralized with a 1M hydrochloric acid solution (4.1 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-

hexane (1:4 - 2:1, v/v). The obtained solid was recrystallized from diethyl ether-hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-3-isopropoxypropoxy)phenyl]-N-(pentylsulfonyl)acrylamide (185 mg, yield: 52%) as colorless crystals. melting point 86-88°C.

Example 457

A mixture of (2E)-3-[1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrrol-2-yl]acrylic acid (600 mg), 1,1'-carbonyldiimidazole (408 mg) and N,N-dimethylformamide (7 ml) was stirred at room temperature for 1 hr. To the mixture were added pentane-1-sulfonamide (336 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.434 ml), and the mixture was stirred at 100°C for 18 hr. After cooling the reaction mixture to room temperature, a 1M hydrochloric acid solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4 - 99:1, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrrol-2-yl]-N-(pentylsulfonyl)acrylamide (545 mg, yield: 64%) as orange crystals. melting point 189-190°C.

Example 458

A mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (498 mg), 4-dimethylaminopyridine (367 mg), and acetonitrile (5 ml) was stirred at room temperature for 10 min. To the mixture were added (2E)-3-[1-(2,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrrol-2-yl]acrylic acid (650 mg) and pentane-1-sulfonamide (308 mg), and the mixture was stirred at room temperature for 4 hr. A 1M hydrochloric acid solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane

(1:5 - 1:3, v/v). The obtained solid was recrystallized from ethyl acetate-hexane to give (2E)-3-[1-(2,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrrol-2-yl]-N-(pentylsulfonyl)acrylamide (481 mg, yield: 53%) as pale-yellow crystals. melting point 170-171°C.

Example 459

To a mixture of (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (989 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (682 mg), 4-dimethylaminopyridine (522 mg) and acetonitrile (4.7 ml) was added pentane-1-sulfonamide (358 mg) at room temperature. The reaction mixture was stirred at room temperature for 16 hr, 1N hydrochloric acid (6 ml), ethyl acetate (15 ml) and water (6 ml) were successively added, and the mixture was stirred at room temperature for 10 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (8 ml). The combined organic layer was washed successively with 1N hydrochloric acid (4 ml) and saturated brine (4 ml), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were dissolved in ethyl acetate, hexane was added and the mixture was stood for 1.5 hr. Hexane (1.5 ml) was further added, and the mixture was stirred for 1.5 hr. The precipitated crystals were collected by filtration with hexane to give (2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (806 mg, yield: 62%) as colorless crystals. The obtained crystals were recrystallized from ethanol to give colorless crystals. melting point 123-125°C. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (3 H, t, J = 7.1 Hz), 1.24 - 1.50 (4 H, m), 1.72 - 1.91 (2 H, m), 3.39 - 3.53 (5 H, m), 3.75 (2 H, dd, J = 5.3, 3.8 Hz), 4.14 (2 H, dd, J = 5.4, 3.7 Hz), 6.37 (1 H, d, J = 15.6 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.90 (1 H,

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dd, J = 8.7, 2.5 Hz), 7.60 (1 H, d, J = 8.7 Hz), 7.80 (1 H, d, J = 15.6 Hz), 8.01 (1 H, s), 8.03 (1 H, d, J = 2.3 Hz), 8.19 - 8.30 (1 H, m).

Example 460

To a solution of (2E)-3-[2-[(5-bromo-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (697 mg) in acetonitrile (15 ml) were added 2-methyl-6-nitrobenzoic anhydride (709 mg), triethylamine (524 mg), 4-dimethylaminopyridine (234 mg) and pentane-1-sulfonamide (286 mg), and the mixture was stirred at room temperature for 40 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethanol-hexane to give (2E)-3-[2-[(5-bromo-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (765 mg, yield: 83%) as colorless crystals. melting point 159.8-160.2°C.

Example 461

To a solution of (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-2-methoxyacrylic acid (450 mg) in acetonitrile (10 ml) were added 2-methyl-6-nitrobenzoic anhydride (404 mg), triethylamine (300 mg), 4-dimethylaminopyridine (118 mg) and pentane-1-sulfonamide (164 mg), and the mixture was stirred at room temperature for 20 hr. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3, v/v) to give (2Z)-3-[2-

{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-2-methoxy-N-(pentylsulfonyl)acrylamide (300 mg, yield: 51%) as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.89 (3 H, t, J = 7.0 Hz), 1.25 - 1.45 (4 H, m), 1.79 - 1.88 (2 H, m), 2.01 - 2.09 (2 H, m), 3.34 (3 H, s), 3.42 - 3.49 (2 H, m), 3.54 (2 H, t, J = 6.1 Hz), 3.66 (3 H, s), 4.08 (2 H, t, J = 6.1 Hz), 6.71 (1 H, d, J = 2.7 Hz), 6.90 (1 H, dd, J = 9.1, 2.7 Hz), 7.17 (1 H, s), 7.91 (1 H, d, J = 9.1 Hz), 8.00 (1 H, d, J = 1.9 Hz), 8.21 (1 H, s), 8.65 (1 H, s).

Example 462

To a solution of tert-butyl [6-(5-(2-methoxyethoxy)-2-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)-5-methylpyridin-3-yl]carbamate (327 mg) in methanol (3 ml) was added 10% hydrogen chloride methanol solution (3 ml), and the mixture was stirred at room temperature for 14 hr and further at 45°C for 3 hr. The reaction mixture was concentrated, and the obtained crude crystals were recrystallized from methanol-diisopropyl ether to give (2E)-3-[2-[(5-amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide dihydrochloride (207 mg, yield: 66%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.80 - 0.85 (3 H, m), 1.14 - 1.29 (4 H, m), 1:30 - 1.49 (2 H, m), 2.39 (3 H, s), 3.09 - 3.27 (4 H, m), 3.30 (3 H, s), 3.65 - 3.67 (2H, m), 4.13 - 4.16 (2 H, m), 6.21 - 6.24 (1 H, m), 6.96 (1 H, dd, J = 8.7, 2.4 Hz), 7.05 (1 H, d, J = 2.4 Hz), 7.39 (1 H, d, J = 8.7 Hz), 7.66 - 7.67 (2 H, m), 11.93 (1 H, s).

Example 463

To a solution of (2E)-3-[2-[(5-amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide dihydrochloride (321 mg) in pyridine (5 ml) were added acetic anhydride (445 mg) and 4-dimethylaminopyridine (145 mg), and the mixture was stirred at room temperature for 7 hr. The reaction mixture was

concentrated, a saturated aqueous ammonium chloride solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate. The obtained crude crystals were recrystallized from ethanol-hexane to give (2E)-3-[2-{[5-(acetylamino)-3-methylpyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (150 mg, yield: 49%) as colorless crystals. melting point 187.9-188.2°C.

Example 464

To a solution of (2E)-3-[2-[(5-amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide dihydrochloride (356 mg) in pyridine (5 ml) were added methanesulfonyl chloride (398 mg) and 4-dimethylaminopyridine (132 mg), and the mixture was stirred at room temperature for 8 hr. The reaction mixture was concentrated, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:1, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-[2-({5-[bis(methylsulfonyl)amino]-3-methylpyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide (100 mg, yield: 24%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.88 (3 H, t, J = 7.1 Hz), 1.25 - 1.41 (4 H, m), 1.75 - 1.88 (2 H, m), 2.44 (3 H, s), 3.40 (6 H, s), 3.43 (3 H, s), 3.43 - 3.45 (2 H, m), 3.72 - 3.75 (2 H, m), 4.11 - 4.14 (2 H, m), 6.28 (1 H, d, J = 15.7 Hz), 6.67 (1 H, d, J = 2.5 Hz), 6.84 (1 H, dd, J = 8.7, 2.5 Hz), 7.53 - 7.56 (2 H, m), 7.82 (1 H, d, J = 15.7 Hz), 7.91 (1 H, d, J = 2.5 Hz), 8.10 (1 H, s).

Example 465

To a solution of 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]propyl (cyclopropylmethyl)carbamate (470 mg) in N,N-dimethylformamide (6 ml) were added ethyl 5,6-dichloronicotinate (476 mg) and potassium carbonate (503 mg), and the mixture was stirred at 80°C for 1 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:2, v/v). The obtained crude crystals were recrystallized from ethyl acetate - hexane to give ethyl 5-chloro-6-[2-[3-({[(cyclopropylmethyl)amino]carbonyl}oxy)propyl]-5-(2-methoxyethoxy)phenoxy]nicotinate (698 mg, yield: 95%) as colorless crystals. melting point 94.6-94.8°C.

Example 466

To a mixed solution of ethyl 5-chloro-6-[2-[3-({[(cyclopropylmethyl)amino]carbonyl}oxy)propyl]-5-(2-methoxyethoxy)phenoxy]nicotinate (297 mg) in tetrahydrofuran (3 ml) and ethanol (3 ml) was added a 1N aqueous sodium hydroxide solution (1.2 ml), and the mixture was stirred at 60°C for 1 hr. After cooling, the reaction mixture was concentrated, and the concentrate was neutralized with 1N hydrochloric acid. Water was poured into the obtained mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2Z)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-2-methoxyacrylic acid (270 mg, yield: 96%) as colorless crystals. melting point 139.5-140.8°C.

Example 467

To a solution of (2E)-3-[2-[(5-bromo-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-N-

(pentylsulfonyl)acrylamide (310 mg) in 1,2-dimethoxyethane (10 ml) were added dihydroxyphenylborane (109 mg), a 2N sodium carbonate aqueous solution (1.2 ml) and tetrakis(triphenylphosphine)palladium (0) (35 mg), and the mixture was heated under reflux for 24 hr. After cooling, water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (2:3, v/v). The obtained crude crystals were recrystallized from ethyl acetate-hexane to give (2E)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-phenylpyridin-2-yl)oxy]phenyl}-N-(pentylsulfonyl)acrylamide (205 mg, yield: 65%) as colorless crystals. melting point 132.8-133.5°C.

Example 468

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]propan-1-ol (0.30 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.11 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.21 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (0.38 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 7:3, v/v) and concentrated to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.008 g, 1%) as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.06 - 1.17 (6 H, m), 1.33 (3 H, s),

1.55 (3 H, s), 1.87 - 2.01 (2 H, m), 2.57 (2 H, t, J = 7.3 Hz), 3.13 - 3.28 (2 H, m), 3.43 - 3.65 (3 H, m), 3.77 (1 H, s), 4.02 - 4.19 (3 H, m), 4.54 (1 H, br.s.), 5.31 - 5.51 (1 H, m), 6.69 (1 H, t, J = 2.6 Hz), 6.76 - 6.87 (1 H, m), 7.12 - 7.23 (1 H, m), 7.42 - 7.65 (1 H, m), 8.01 (1 H, s), 8.28 (1 H, s).

Example 469

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]propan-1-ol (0.30 g) in acetonitrile (5 ml) was added chlorosulfonylisocyanate (0.11 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (0.21 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-(Aminoethyl)pyridine (0.45 g) was added, and the mixture was stirred while warming to room temperature over 12 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 7:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate (0.043 g, 9%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.54 (6 H, s), 1.78 - 2.00 (2 H, m), 2.43 - 2.61 (2 H, m), 2.93 - 3.12 (2 H, m), 3.40 - 3.60 (2 H, m), 3.93 - 4.19 (4 H, m), 4.37 - 4.62 (2 H, m), 6.42 (1 H, br.s.), 6.66 (1 H, dd, J = 11.7, 2.4 Hz), 6.71 - 6.86 (1 H, m), 7.01 - 7.22 (3 H, m), 7.52 - 7.67 (1 H, m), 7.99 (1 H, t, J = 2.5 Hz), 8.21 - 8.31 (1 H, m), 8.44 - 8.54 (1 H, m).

Example 470

(2E)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (0.30 g), N-[(5-methylpyrazin-2-yl)methyl]sulfamide (0.16 g), 1-ethyl-3-

(3-dimethylaminopropyl)carbodiimide hydrochloride (0.17 g), 4-dimethylaminopyridine (0.11 g) and N,N-dimethylformamide (5 ml) were mixed, and the mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (2:8 - 1:0, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-({[(5-methylpyrazin-2-yl)methyl]amino}sulfonyl)acrylamide (0.030 g, 7%) as colorless crystals. melting point 126-128°C.

Example 471

(2E)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (0.30 g), N-(2-pyridin-2-ylethyl)sulfamide (0.16 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.17 g), 4-dimethylaminopyridine (0.11 g) and N,N-dimethylformamide (5 ml) were mixed, and the mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 7:3, v/v), concentrated, and crystallized from ethyl acetate-hexane to give (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-{[(2-pyridin-2-ylethyl)amino]sulfonyl}acrylamide (0.077 g, 18%) as colorless crystals. melting point 121-123°C.

Example 472

(2E)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methylacrylic acid (0.30 g), pyrrolidine-1-sulfonamide (0.12 g), 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (0.17 g), 4-dimethylaminopyridine (0.11 g) and N,N-dimethylformamide (5 ml) were mixed, and the mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 1:1, v/v), and concentrated to give (2E)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-2-methyl-N-(pyrrolidin-1-ylsulfonyl)acrylamide (0.10 g, 26%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.36 (6 H, d, J = 6.0 Hz), 1.89 (4 H, br.s.), 1.99 - 2.12 (3 H, m), 3.49 (4 H, br.s.), 4.45 - 4.64 (1 H, m), 6.71 (1 H, d, J = 2.3 Hz), 6.84 (1 H, dd, J = 8.7, 2.4 Hz), 7.18 - 7.38 (2 H, m), 7.86 - 8.04 (2 H, m), 8.25 (1 H, d, J = 1.1 Hz).

Example 473

To a solution of 3-(4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propan-1-ol (465 mg) in toluene (12 ml) was added chlorosulfonylisocyanate (171 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (273 mg) was added to the reaction mixture and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (713 mg) was added, and the mixture was stirred at room temperature for 2.5 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 1:1, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-(4-butoxy-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (430 mg, yield:

61%) as colorless crystals. melting point 91.4-91.6°C.

Example 474

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propan-1-ol (452 mg) in toluene (11 ml) was added chlorosulfonylisocyanate (160 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (255 mg) was added to the reaction mixture and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (667 mg) was added, and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:3 - 1:1, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (298 mg, yield: 44%) as colorless crystals. melting point 67.4-68.0°C.

Example 475

To a solution of 3-(4-(but-3-en-1-yloxy)-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propan-1-ol (402 mg) in toluene (10 ml) was added chlorosulfonylisocyanate (148 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (237 mg) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (619 mg) was added, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 2:3, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-(4-(but-3-en-1-yloxy)-2-{[3-

chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (399 mg, yield: 65%) as colorless crystals. melting point 111.1-113.0°C.

Example 476

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-furylmethoxy)phenyl]propan-1-ol (424 mg) in toluene (10 ml) was added chlorosulfonylisocyanate (147 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (235 mg) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (614 mg) was added, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (3:7 - 1:1, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-furylmethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (359 mg, yield: 57%) as colorless crystals. melting point 118.0-119.8°C.

Example 477

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-morpholin-4-ylethoxy)phenyl]propan-1-ol (600 mg) in acetonitrile (13 ml) was added chlorosulfonylisocyanate (194 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (309 mg) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (807 mg) was added, and the mixture was stirred at room temperature for 60 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and

eluted with ethyl acetate-hexane (1:1 - 9:1, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-morpholin-4-ylethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (376 mg, yield: 43%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.13 (6 H, d, J = 6.0 Hz), 1.86 - 2.07 (2 H, m), 2.49 - 2.63 (6 H, m), 2.80 (2 H, t, J = 5.6 Hz), 3.17 - 3.26 (2 H, m), 3.48 - 3.62 (3 H, m), 3.69 - 3.76 (4 H, m), 4.05 - 4.19 (4 H, m), 5.43 (1 H, br. s.), 6.64 - 6.68 (1 H, m), 6.77 - 6.82 (1 H, m), 7.17 (1 H, d, J = 8.7 Hz), 8.01 (1 H, d, J = 1.7 Hz), 8.25 - 8.29 (1 H, m).

Example 478

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]propan-1-ol (383 mg) in toluene (8.9 ml) was added chlorosulfonylisocyanate (132 mg) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (210 mg) was added to the reaction mixture, and the mixture was stirred for 1 hr. 2-Aminoethyl isopropyl ether (549 mg) was added, and the mixture was stirred at room temperature for 60 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (7:13 - 7:3, v/v) to give colorless crystals. Recrystallization from ethyl acetate-hexane gave 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(tetrahydrofuran-2-ylmethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (246 mg, yield: 45%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.13 (6 H, d, J = 6.0 Hz), 1.68 - 1.83 (2 H, m), 1.86 - 2.12 (4 H, m), 2.55 (2 H, t, J = 7.3 Hz), 3.23 (2 H, d, J = 4.3 Hz), 3.44 - 3.62 (3 H, m), 3.76 - 3.96 (4 H, m), 4.14 (2 H, t, J = 6.4 Hz), 4.21 - 4.30 (1 H, m), 5.43 (1

H, d, J = 1.7 Hz), 6.67 (1 H, d, J = 2.4 Hz), 6.82 (1 H, dd, J = 8.5, 2.6 Hz), 7.18 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 2.3 Hz), 8.27 (1 H, dd, J = 2.2, 1.0 Hz).

Example 479

To a solution of 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)propan-1-ol (10.9 g) in acetonitrile (150 ml) was added chlorosulfonylisocyanate (2.95 g) under ice-cooling, and the mixture was stirred for 30 min. Pyridine (5.9 ml) was added to the reaction mixture, and the mixture was stirred for 1 hr. (2-Aminoethyl)isopropyl ether (10.8 g) was added, and the mixture was stirred while warming to room temperature over 6 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was concentrated. Water was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated.

To a solution of the residue in tetrahydrofuran (100 ml) was added a 1.0M tetra-n-butylammnonium fluoride tetrahydrofuran solution (100 ml), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, water was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel column chromatography, eluted with ethyl acetate-hexane (0:1 - 2:8, v/v), concentrated and crystallized from ethyl acetate-hexane. The obtained crystals were subjected to HPLC (acetonitrile:water, containing 0.01% TFA, 5:95 - 100:0, v/v) and further crystallized from ethyl acetate-hexane to give 3-(4-{2-[(aminosulfonyl)oxy]ethoxy}-2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate (0.18 g, 1%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.14 (6 H, d, J = 6.1 Hz), 1.87 - 2.02 (2 H, m), 2.61 (2 H, t, J = 7.0 Hz), 3.16 - 3.27 (2 H, m), 3.48 - 3.64 (3 H, m), 4.11 - 4.18 (2 H, m), 4.23 - 4.32 (2 H, m), 4.52 (2 H, dd, J = 5.3, 3.4 Hz), 4.98 (2 H, br.s.), 5.38 (1 H, t, J = 5.7 Hz), 6.71 (1 H, d, J = 2.7 Hz), 6.82 (1 H, dd, J = 8.7, 2.7 Hz), 7.22 (1 H, d, J = 8.7 Hz), 7.77 (1 H, s), 8.03 (1 H, d, J = 2.3 Hz), 8.28 (1 H, s).

Experimental Example 1

Blood glucose and blood lipid (triglyceride) lowering action in mice

The test compound was mixed with a powder diet (CE-2, CLEA JAPAN, INC.) at a proportion of 0.01% (0.03% for the compounds of Examples 1, 2, 12, 81, 94, 96, 129 and 143, and 0.005% for the compounds of Examples 28, 30 and 37) and freely given to KKAy mice (9 to 14-week-old, 5 mice per group) which are obesity non-insulin-dependent diabetes (type-2 diabetes) models, for 4 to 7 days. During this period, water was freely given. The blood was drawn from the orbital venous plexus. Glucose and triglyceride in the plasma separated from the blood were quantitated using L Type Wako Glu2 (Wako Pure Chemical Industries, Ltd.) and L Type Wako TG·H (Wako Pure Chemical Industries, Ltd.), respectively, according to an enzyme method. The results are shown in Table 1.

In the Table, the "hypoglycemic action (%)" shows a relative value (%) of the blood glucose level of the test compound administration group when the blood glucose level of the test compound non-administration group is 100%. In addition, the "hypolipidemic action (%)" shows a relative value (%) of the blood triglyceride of the test compound administration group when the blood triglyceride value of the test compound non-administration group is 100%.

Table 1

test compound (Example No.)	hypoglycemic action (%)	hypolipidemic action (%)
1	47	53
2	50	41
12	46	43
26	50	62
28	52	32
30	47	57
37	68	70
58	64	73
81	44	60
94	48	79
96	53	57
97	58	64
112	53	70
129	45	76
143	47	76
151	59	73
155	70	70
183	48	44
196	54	79
197	58	87
198	62	84
204	52	36
205	54	50
207	54	43
208	70	71
210	58	69
211	49	46
214	56	65
218	81	129
250	78	121
252	46	20
424	70	18

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429	51	60
430	45	34
437	45	58
439	49	34
444	55	52

As shown above, it is clear that the compound of the present invention has superior hypoglycemic action and hypolipidemic action, and is useful as an agent for the prophylaxis or treatment of diabetes, hyperlipidemia (particularly, hypertriglyceridemia), impaired glucose tolerance and the like.

Experimental Example 2 ($PPAR\gamma$-$RXR\alpha$ heterodimer ligand activity)

The $PPAR\gamma$:$RXR\alpha$:4ERPP/CHO-K1 cells described in WO03/099793 were cultured in a Ham F12 medium [manufactured by Life Technologies, Inc., US] containing 10% calf fetal serum [manufactured by Life Technologies, Inc., US], sown in a 96-well white plate [manufactured by Corning Coster Corporation, US] at 1×10^4 cells/well, and incubated overnight in a carbon dioxide gas incubator at 37°C.

Then, the medium was removed from the 96 well white plate, 45 μl of Ham F12 medium containing 0.1% fatty acid-free bovine serum albumin (BSA) and a test compound (5 μl) were added, and the cells were incubated for one day in a carbon dioxide gas incubator at 37°C. The medium was removed, 20 μl of PicaGene 7.5 (manufactured by Wako Pure Chemical Industries, Ltd.) 2-fold diluted with HBSS (HANKS' BALANCED SALT SOLUTION) [manufactured by BIO WHITTAKER, US] was added. After stirring, the luciferase activity was determined using the 1420 ARVO Multilabel Counter [manufactured by PerkinElmer, US].

The induction rate was calculated from the luciferase activity of each test compound based on the luciferase activity of the test compound non-administration group as 1. The test compound concentration and the induction rate were analyzed by PRISM [manufactured by GraphPad Software, Inc.,

US] to calculate EC_{50} value (compound concentration showing 50% of the maximum value of induction rate) of the test compound. The results are shown in Table 2.

Table 2

test compound (Example No.)	EC_{50} (nM)
1	1.5
2	2.6
12	15
13	26
26	4.6
28	4.5
30	3.8
32	6.6
37	21
44	6.9
47	3.4
51	20
58	10
64	8.7
81	16
94	20
96	8.4
97	7.5
111	9.3
112	8.3
129	10
151	7.2
155	12
173	9.8
183	3.8
190	15
196	4.4
197	28
198	7.8

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199	13
204	0.92
205	3.1
207	0.99
208	4.0
209	2.3
210	6.7
211	5.2
214	1.1
218	80
223	55
224	16
225	16
226	8.5
248	18
250	7.2
251	7.4
252	3.1
255	3.9
256	13
257	2.1
258	1.1
371	4.7
424	6.2
427	22
429	3.8
430	0.95
437	54
439	1.8
444	3.4
446	13
451	15
453	7.3

As shown above, it is clear that the compound of the present invention has superior PPARγ-RXRα heterodimer ligand

activity.

Formulation Example 1 (production of capsule)

1)	compound of Example 1	30 mg
2)	finely divided powder cellulose	10 mg
3)	lactose	19 mg
4)	magnesium stearate	1 mg
	total	60 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablet)

1)	compound of Example 1	30 g
2)	lactose	50 g
3)	cornstarch	15 g
4)	calcium carboxymethylcellulose	44 g
5)	magnesium stearate	1 g
	1000 tablets total	140 g

The total amount of 1), 2), 3) and 30 g of 4) are kneaded with water, vacuum dried and sized. The sized powder is mixed with 14 g of 4) and 1 g of 5) and the mixture is punched out with a tableting machine. In this way, 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

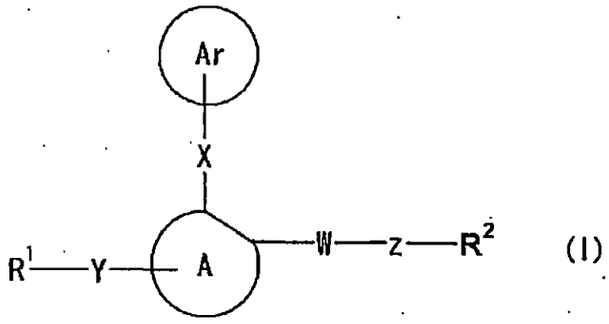
INDUSTRIAL APPLICABILITY

The compound of the present invention is useful as an agent for the prophylaxis or treatment of diabetes, which is associated with a fewer side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like.

This application is based on a patent application No. 2005-232646 filed in Japan, the contents of which are incorporated in full herein by this reference.

CLAIMS

1. An agent for the prophylaxis or treatment of diabetes, which comprises a compound represented by the formula:



(I)

wherein ring A is an aromatic ring which is optionally further substituted;

Ar is an optionally substituted monocyclic ring;

R^1 is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a spacer having a main chain of 1 or 2 atoms;

Y is a bond or a spacer having a main chain of 1 or 2 atoms;

W is an optionally substituted divalent hydrocarbon group having 1 to 20 carbon atoms;

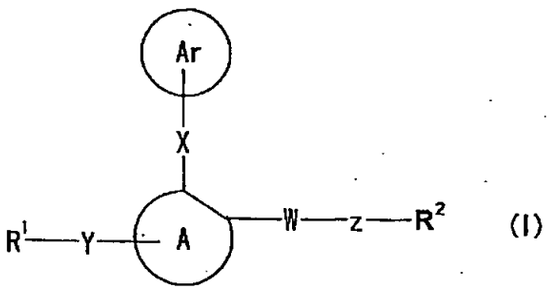
Z is $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$, $-NR^aSO_2NR^bCOO-$ or $-CONR^aSO_2NR^c-$ (R^a and R^b are each independently a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group, R^c is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group, or R^c and R^2 are bonded to each other to form, together with the adjacent nitrogen atom, an optionally substituted, nitrogen-containing heterocycle),

or a salt thereof or a prodrug thereof.

2. An insulin sensitizer comprising the compound of claim 1 or a salt thereof or a prodrug thereof.

3. The agent of claim 1, wherein Ar is an optionally substituted monocyclic aromatic ring.

4. A compound represented by the formula:



(I)

wherein ring A, Ar, R^1, R^2, X, Y, W, Z are as defined in claim 1 (provided that Ar is not an unsubstituted benzene ring), or a salt thereof, which excludes the following compounds:
(4-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)-3-{[3-(quinolin-2-ylmethoxy)benzyl]oxy}phenoxy)acetic acid,
ethyl (4-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)-3-{[3-(quinolin-2-ylmethoxy)benzyl]oxy}phenoxy)acetate,
1-{4-methoxy-2-[(4-vinylbenzyl)oxy]phenyl}ethyl [4-(diethylamino)-2-methylphenyl]carbamate,
N-{2-[4,5-dimethoxy-2-(2-thienylcarbonyl)phenyl]ethyl}-N,4-dimethylbenzenesulfonamide,
N-(2,2-dimethoxyethyl)-N-{3-[6-({(2,2-dimethoxyethyl)[(4-methylphenyl)sulfonyl]amino}methyl)-2,3-dimethoxyphenoxy]-4-methoxybenzyl}-4-methylbenzenesulfonamide, and
2-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-dimethoxybenzyl phenylcarbamate.

5. The compound of claim 4, wherein Ar is an optionally substituted monocyclic aromatic ring, or a salt thereof.

6. The compound of claim 4, wherein Ar is an optionally substituted 5- or 6-membered monocyclic aromatic heterocycle,

or a salt thereof.

7. The compound of claim 4, wherein Ar is a substituted benzene ring, or a salt thereof.

8. The compound of claim 4, wherein X is an oxygen atom, or a salt thereof.

9. The compound of claim 4, wherein Z is $-CONR^aSO_2-$, or a salt thereof.

10. The compound of claim 4, wherein R^1 is

(1) a C_{1-10} alkyl group or a C_{2-10} alkenyl group, each optionally substituted by 1 to 3 substituents selected from

a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group;

a carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group;

an aromatic heterocyclic group optionally substituted by a C_{1-6} alkyl group;

a non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

a C_{1-6} alkoxy-carbonyl group;

a carboxyl group;

a hydroxy group;

a cyano group;

a silyloxy group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and a C_{6-14} aryl group;

a C_{1-6} alkyl-carbonyloxy group;

a C_{3-10} cycloalkyloxy group;

a C_{3-10} cycloalkyl-C_{1-6} alkyloxy group;

a C_{1-6} alkylsulfonyl group;

a C_{1-6} alkyl-carbonyl group; and

a sulfamoyloxy group;

(2) a C_{3-10} cycloalkyl group;

(3) a C_{6-14} aryl group;

(4) a C_{7-13} aralkyl group;

(5) a C_{3-10} cycloalkyl-C_{1-6} alkyl group;

(6) a monocyclic non-aromatic heterocyclic group; or

(7) a monocyclic aromatic heterocyclic group, or a salt thereof.

11. The compound of claim 4, wherein R^2 is

(1) a hydrogen atom;

(2) a C_{1-10} alkyl group or a C_{2-10} alkenyl group, each optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group; a halogen atom; a hydroxy group; a cyano group; a C_{1-6} alkylthio group; a carbamoyl group; a C_{6-14} aryloxy group; an amino group optionally substituted by 1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{1-6} alkyl-carbonyl group and a C_{6-14} aryl group; an aromatic heterocyclic group optionally substituted by 1 to 3 C_{1-6} alkyl group; and a non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group;

(3) a C_{3-10} cycloalkyl group optionally substituted by a C_{1-6} alkyl group and optionally condensed with a benzene ring;

(4) a C_{6-14} aryl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy group, a C_{1-6} alkoxy group, a halogen atom, a nitro group, and a cyano group;

(5) a C_{7-13} aralkyl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy group and a C_{6-14} aryl group;

(6) a C_{3-10} cycloalkyl-C_{1-6} alkyl group; or

(7) a non-aromatic heterocyclic group optionally substituted by an oxo group, or a salt thereof.

12. The compound of claim 4, wherein ring A is a benzene ring

or a 5- or 6-membered aromatic heterocycle, or a salt thereof.

13. The compound of claim 4, wherein Y is a bond, -O- or $-SO_2-$, or a salt thereof.

14. The compound of claim 4, wherein W is C_{1-6} alkylene or C_{2-6} alkenylene, or a salt thereof.

15. The compound of claim 4, which is

3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-N-(pentylsulfonyl)propanamide,

(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-(pentylsulfonyl)acrylamide,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (pentylsulfonyl)carbamate,

3-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]-N-(pentylsulfonyl)propanamide,

3-{3-tert-butyl-1-[2-chloro-4-(trifluoromethyl)benzyl]-1H-pyrazol-5-yl}-N-(pentylsulfonyl)propanamide,

butyl ({2-[3-butoxy-1-(2,4-dichlorobenzyl)-1H-pyrazol-5-yl]ethyl}sulfonyl)carbamate,

(2E)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-ethoxy-1-(ethoxymethyl)ethoxy]phenyl}-N-(pentylsulfonyl)acrylamide,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl {[(2-pyridin-2-ylethyl)amino]sulfonyl}carbamate,

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-N-[(pentylamino)sulfonyl]propanamide,

(2E)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]-N-

(pentylsulfonyl)acrylamide or

3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxyethoxy)phenyl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate,

or a salt thereof.

16. A prodrug of the compound of claim 4 or a salt thereof.

17. A pharmaceutical agent comprising the compound of claim 4 or a salt thereof or a prodrug thereof.

18. A method for the prophylaxis or treatment of diabetes in a mammal, which comprises administering the compound of claim 1 or a salt thereof or a prodrug thereof to the mammal.

19. A method of improving insulin resistance in a mammal, which comprises administering the compound of claim 1 or a salt thereof or a prodrug thereof to the mammal.

20. Use of the compound of claim 1 or a salt thereof or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes.

21. Use of the compound of claim 1 or a salt thereof or a prodrug thereof for the production of an insulin sensitizer.

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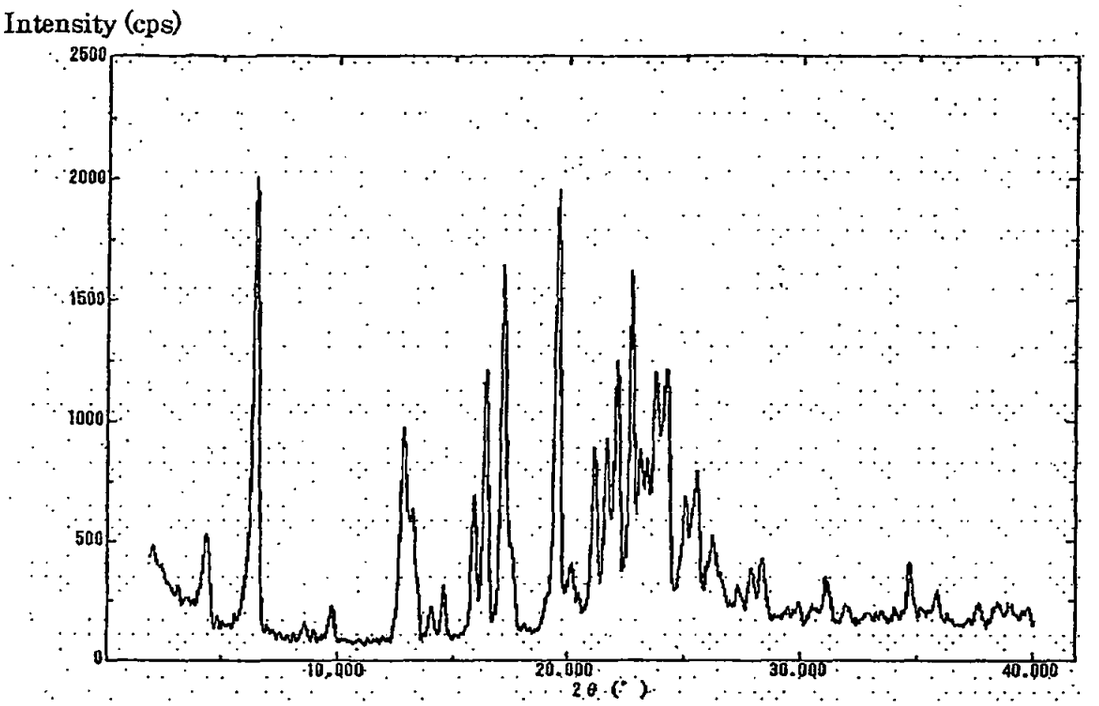
Intensity (cps)
2500
2000
1500
1000
500
0
10.000
20.000
30.000
40.000
2θ (°)

FIG. 1

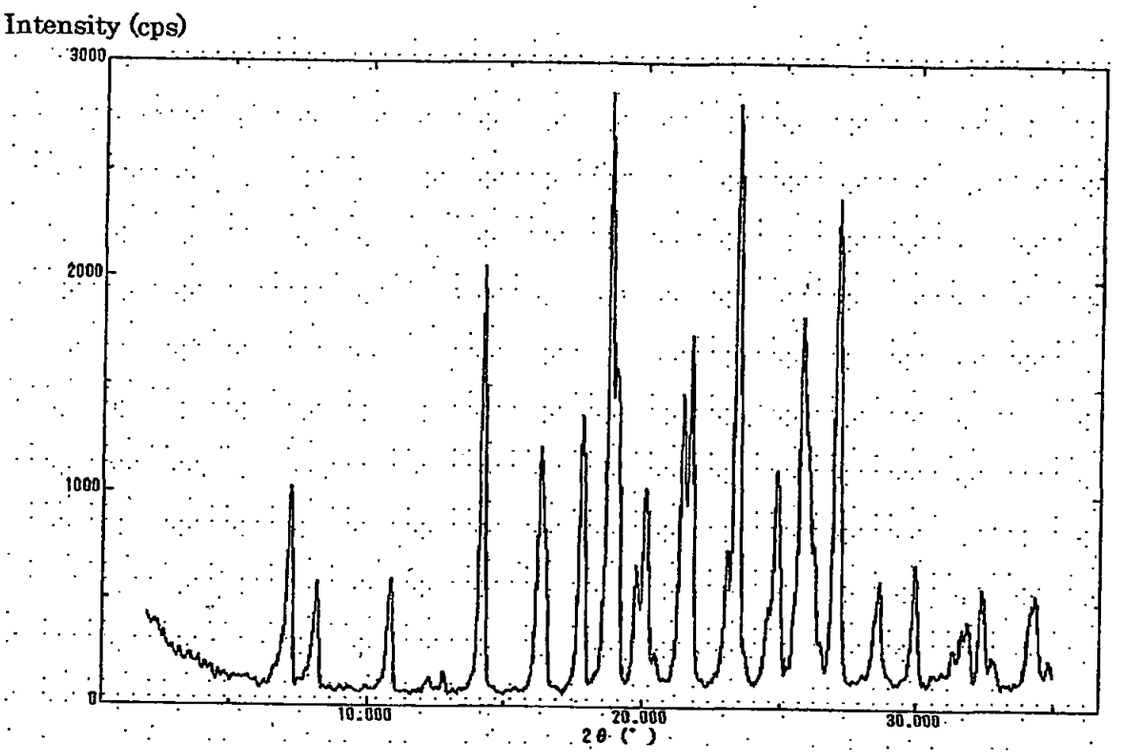

FIG. 2

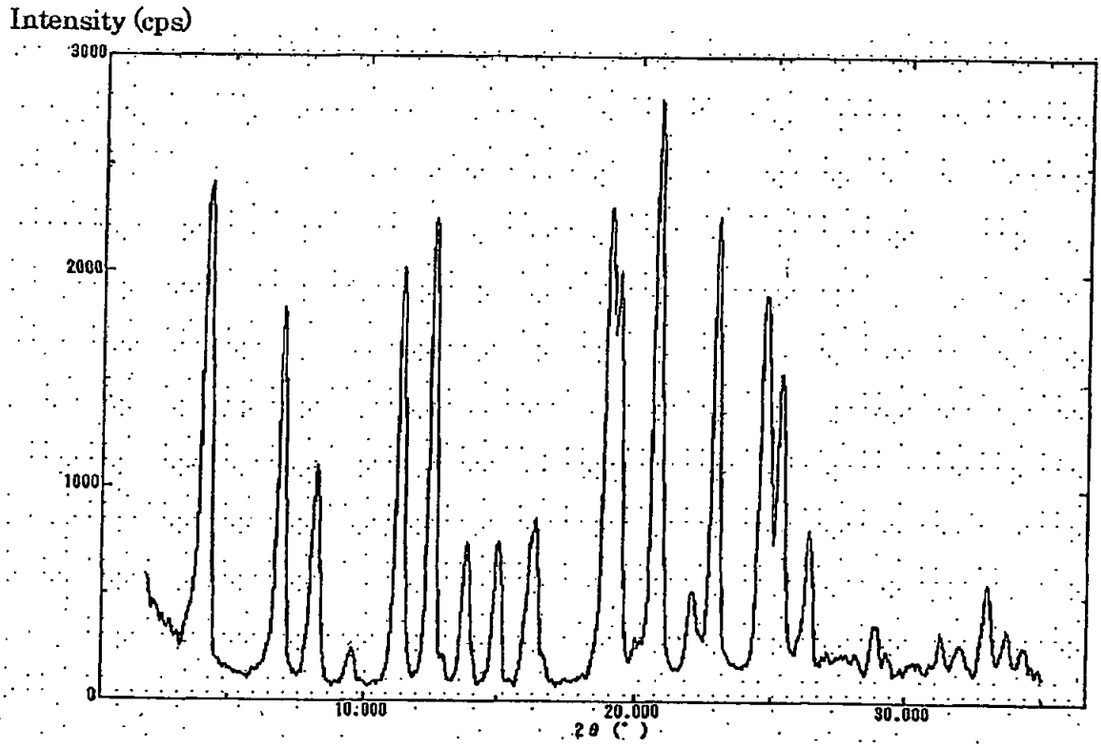

FIG. 3

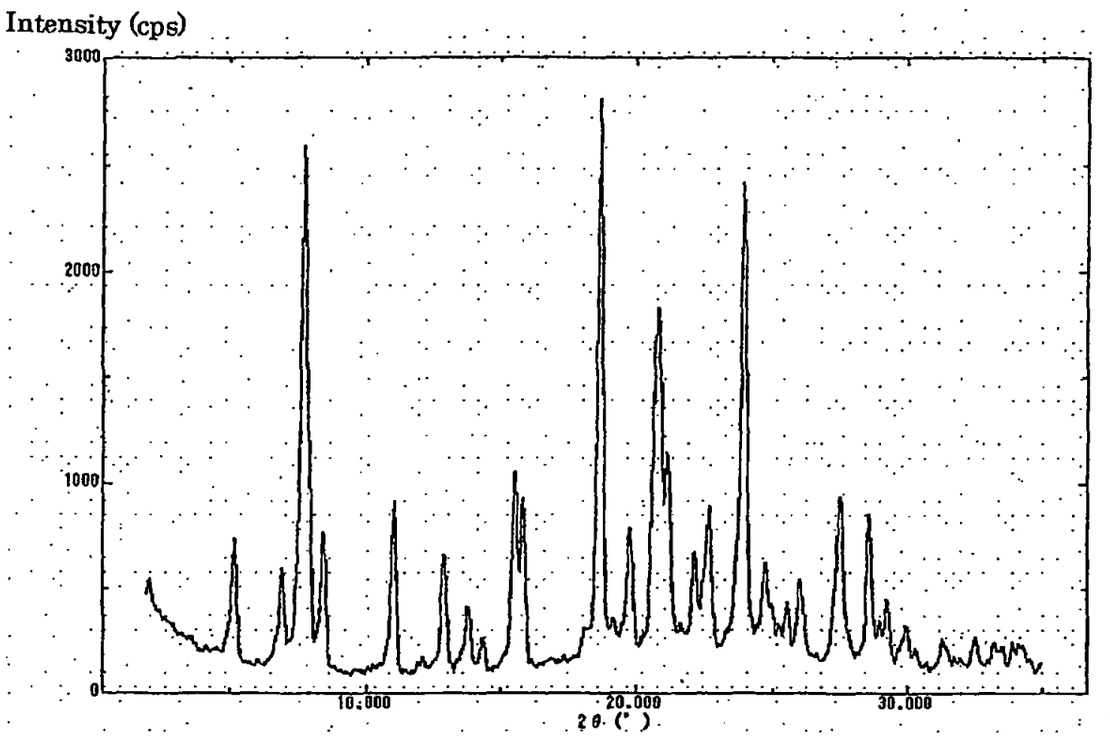

FIG. 4

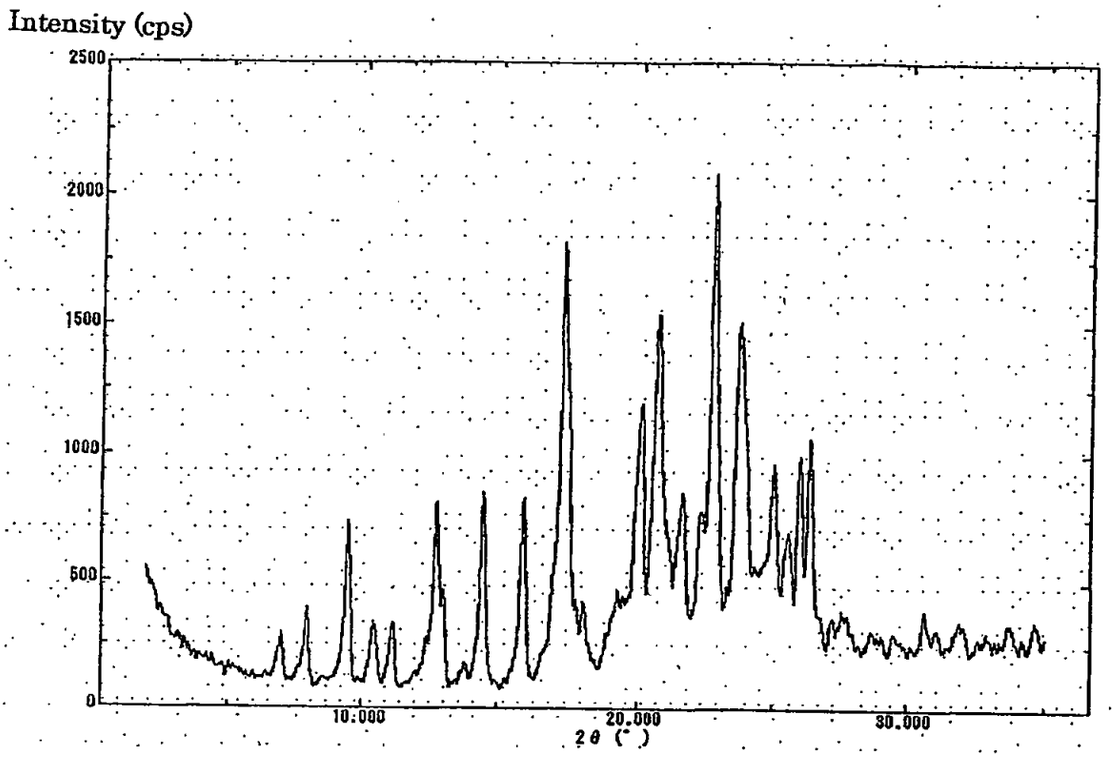

FIG. 5

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AGENTE TERAPEUTICO PARA DIABETES

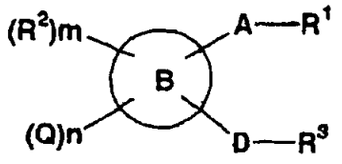
CAMPO DE LA INVENCION

La presente invención se refiere a compuestos aromáticos útiles como agentes terapéuticos para diabetes.

ANTECEDENTES DE LA INVENCION

Como compuestos aromáticos, se conocen los compuestos descritos en la siguiente bibliografía.

(1) Como un agente terapéutico para el dolor y similares, la referencia de patente 1 (WO 2003/016254) describe un compuesto representado por la fórmula:



(I)

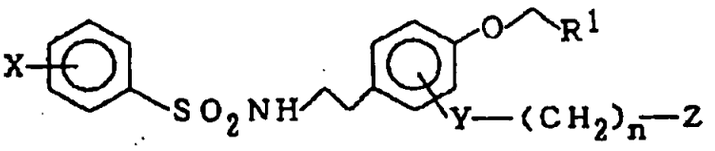
en donde R^1 es COOH, $COOR^4$ (R^4 es alquilo, etc.) y similares; A es alquileno y similares; R^2 es alquilo y similares; m es 0, 1 ó 2; B es un anillo benceno y similares; Q es alquilen-Cyc2 (Cyc2 es heterociclo, etc.), un anillo alquilen-O-benceno y similares; n es 0, 1 ó 2; D es O-alquileno, NHCO-alquileno y similares; y R^3 es un anillo benceno, un anillo naftaleno y similares, que tiene acción antagonista de receptor de prostaglandina E2.

(2) Como un agente terapéutico para dolor, retinopatía diabética y similares, la referencia de patente 2 (WO99/47497) describe un compuesto representado por la fórmula:

(I)

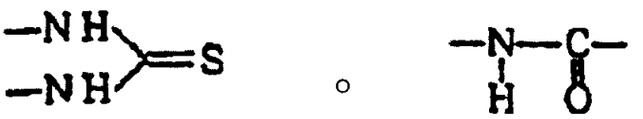
en donde HET es un anillo aromático monocíclico o bicíclico de 5 a 12 miembros; R^1, R^2 y R^3 son cada uno independientemente H, halógeno, alquilo inferior y similares; A es O, S(O)n y similares; B es $-(C(R^{18})_2)p-Y-(C(R^{18})_2)q-$ (p y q son cada uno independientemente 0-3); X es un grupo arilo monocíclico de 5 a 10 miembros o un grupo heteroarilo o un grupo arilo bicíclico o un grupo heteroarilo con 1-3 heteroátomos seleccionados de O, S(O)n y N(O)m, que es sustituido con R^{14} y R^{15} según sea necesario, (A y B están unidos al grupo arilo o grupo heteroarilo, y están en posición orto entre sí); Y es O, S(O)n, NR^{17}, un enlace o $-CR^{18}=CR^{18}-$; Z es OH o $NHSO_2R^{19}$; R^{17} son cada uno independientemente H, alquilo inferior o Bn; R^{18} son cada uno independientemente H, F, alquilo inferior y similares; R^{19} es alquilo inferior, alquenilo inferior, alquinilo inferior, CF_3, $HET(R^a)_{4-9}$, alquilo inferior-$HET(R^a)_{4-9}$ o alquinilo inferior-$HET(R^a)_{4-9}$; y R^a es H, OH, halógeno, CN, NO_2, amino, alquilo de C_{1-6}, alquenilo de C_{1-6}, alquinilo de C_{1-6}, alcoxi de C_{1-6} y similares, que es un ligando receptor de prostaglandina.

(3) Como un agente terapéutico para trombosis, asma y similares, la referencia de patente 4 (EP-A-562796) describe un compuesto representado por la fórmula:

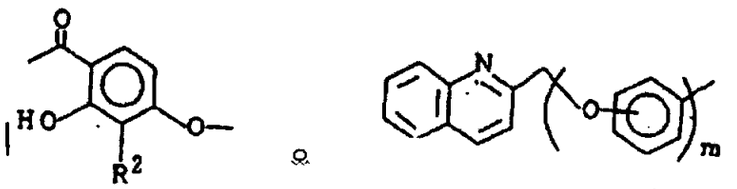


(I)

en donde X es un átomo de hidrógeno, un grupo alquilo inferior o un átomo de halógeno; R^1 es un grupo carboxilo o un grupo alcoxi inferior carbonilo; Y es un átomo de oxígeno,

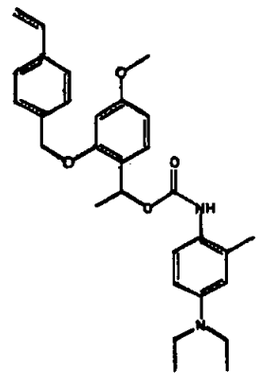


; n es un número entero de 0-5; Z es

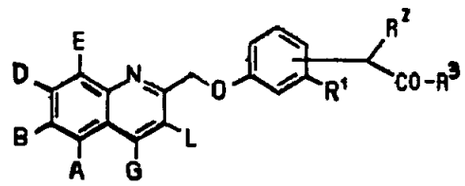


; R^2 es un átomo de hidrógeno o un grupo alquilo inferior; y m es 0 ó 1, que es un antagonista de tromboxano A2 y un antagonista de leucotrieno.

(4) Como un material de partida para un polímero útil como solución de desarrollo (agente de desarrollo), la referencia de patente 5 (US-A-2004/137380) describe un compuesto representado por la fórmula:

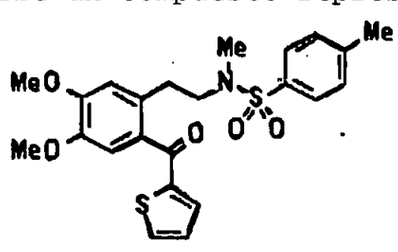


(5) Como un agente terapéutico para la inflamación, la referencia de patente 6 (patente de los Estados Unidos No. 5597833) describe un compuesto representado por la fórmula:

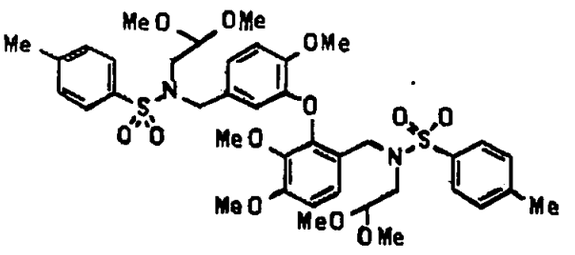


en donde A, B, D, E, G y L son cada uno independientemente H y similares; R^1 es halógeno, no más de alquilo de C_8, alquenilo y similares (estos son sustituidos por fenilo, etc., según sea necesario); R^2 es H y similares; R^3 es OH, $NR^4SO_2R^5$ y similares; R^4 es H y similares; R^5 es CF_3, fenilo y similares, que tienen acción inhibitoria de 5-lipoxigenasa.

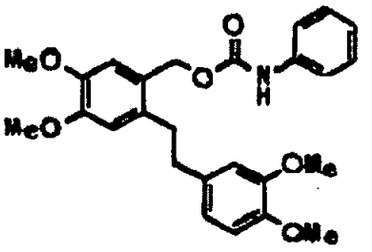
(6) Como un intermediario de la síntesis de isoquinolina, la referencia no de patente 1 (Perkin Trans, 1, 275 (1985)) describe un compuesto representado por la fórmula:



(7) La referencia no de patente 2 (Archiv der Pharmazie, 316(6), 694-6 (1983)) describe un compuesto representado por la fórmula:



(8) La referencia no de patente 3 (Arch Pharm., 141 (1964)) describe un compuesto representado por la fórmula:



El receptor gamma activado por proliferador de peroxisoma (PPARγ), que es un miembro de la superfamilia de receptores de hormonas nucleares representada por los receptores de hormonas esteroides y los receptores de hormonas de glándulas tiroides, muestra una expresión inducida al comienzo de la diferenciación de adipocitos y juega un importante papel como regulador maestro en la diferenciación de adipocitos. PPARγ se une a un ligando para formar un dímero con receptor de retinoide X (RXR), y el dímero se fija a un elemento de respuesta de un gen blanco en núcleo para

controlar directamente (activar) la eficiencia de la transcripción.

En años recientes, se ha sugerido la posibilidad de que 15-desoxi-Δ12,14 prostaglandina J2, que es un metabolito de prostaglandina D2, es un ligando endógeno de PPARγ, y además, se ha aclarado que ciertos sensibilizadores de insulina representados por derivados de tiazolidinodiona tienen actividad de ligando de PPARγ y la fuerza de la actividad es paralela a una acción hipoglicémico o acción promotora de la diferenciación de adipocitos [referencia no de patente 4 (Cell, 83, 803 (1995)); referencia no de patente 5 (The Journal of Biological Chemistry, 270, 12953(1995)); referencia no de patente 6 (Journal of Medicinal Chemistry, 39, 665 (1996))].

También, se ha descubierto que 1) PPARγ se expresa en la célula cultivada derivada de liposarcoma humano y la adición de ligando PPARγ detiene su crecimiento [referencia no de patente 7 (Proceedings of The National Academy of Sciences of The United States of America, 94, 237 (1997))]; 2) los fármacos antiinflamatorios no esteroides representados por indometacina y fenoprofeno tienen actividad de ligando de PPARγ [referencia no de patente 8 (The Journal of Biological Chemistry, 272, 3406 (1997))]; 3) PPARγ tiene gran expresión en macrófagos activados, y la adición de su ligando conduce a la inhibición de la transcripción del gen que interviene en la inflamación [referencia no de patente 9 (Nature, 391, 79

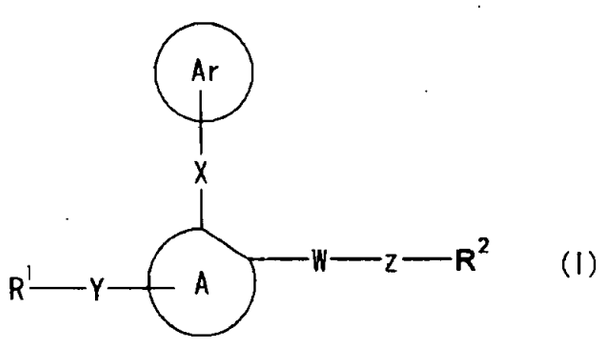
(1998))]; 4) el ligando PPARγ inhibe la producción de citocinas inflamatorias por los monocitos (TNFα, IL-1β, IL-6) [referencia no de patente 10 (Nature, 391, 82 (1998))] y similares.

BREVE DESCRIPCION DE LA INVENCION

Hay una demanda de desarrollo de un agente para la prevención o el tratamiento de diabetes, que se asocia con menos efectos secundarios, por ejemplo aumento de peso corporal, acumulación de adipocitos, hipertrofia cardiaca y similares.

Los presentes inventores descubrieron que un compuesto representado por la siguiente fórmula (I) tiene acción hipoglicémico superior, y es útil para la prevención y el tratamiento de diabetes, que resultó en la realización de la presente invención. En consecuencia, la presente invención se refiere a lo siguiente.

[1] Un agente para la prevención o el tratamiento de diabetes, que comprende un compuesto representado por la fórmula:



(I)

en donde el anillo A es un anillo aromático que está además opcionalmente sustituido;

Ar es un anillo monocíclico opcionalmente sustituido;

R^1 es un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido;

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido;

X es un espaciador que tiene una cadena principal de 1 ó 2 átomos;

Y es un enlace o un espaciador con una cadena principal de 1 ó 2 átomos;

W es un grupo hidrocarburo divalente opcionalmente sustituido con 1 a 20 átomos de carbono;

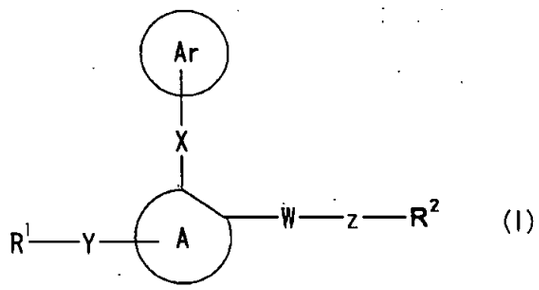
Z es $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$, $-NR^aSO_2NR^bCOO-$ o $-CONR^aSO_2NR^c-$ (R^a y R^b son cada uno, de manera independiente, un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, R^c es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, o R^c y R^2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo opcionalmente sustituido con contenido de nitrógeno),

o una de sus sales (de ahora en adelante, a veces denominado compuesto (I)) o uno de sus profármacos.

[2] Un sensibilizador de insulina que comprende el compuesto (I) o uno de sus profármacos.

[3] El agente de [1] antes mencionado, en donde Ar es un anillo aromático monocíclico opcionalmente sustituido.

[4] Un compuesto representado por la fórmula:



(I)

en donde el anillo A, Ar, R^1, R^2, X, Y, W, Z son como se definen en el [1] antes mencionado (con la condición de que Ar no sea un anillo benceno no sustituido),

o una de sus sales, que excluye los siguientes compuestos:

ácido (4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acético,

(4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acetato de etilo,

[4-(dietilamino)-2-metilfenil]carbamato de 1-{4-metoxi-2-[(4-vinilbencil)oxi]fenil}etilo,

N-{2-[4,5-dimetoxi-2-(2-tienilcarbonil)fenil]etil}-N,4-dimetilbencensulfonamida,

N-(2,2-dimetoxietil)-N-{3-[6-({(2,2-dimetoxietil)[(4-metilfenil)sulfonil]amino}metil)-2,3-

dimetoxifenoxi]-4-metoxibencil}-4-metilbencensulfonamida, y

fenilcarbamato de 2-[2-(3,4-dimetoxifenil)etil]-4,5-dimetoxibencilo.

[5] El compuesto de [4] antes mencionado, en donde Ar es un anillo aromático monocíclico opcionalmente sustituido, o una de sus sales.

[6] El compuesto de [4] antes mencionado, en donde Ar es un heterociclo aromático monocíclico de 5 ó 6 miembros opcionalmente sustituido, o una de sus sales.

[7] El compuesto de [4] antes mencionado, en donde Ar es un anillo benceno sustituido, o una de sus sales.

[8] El compuesto de [4] antes mencionado, en donde X es un átomo de oxígeno, o una de sus sales.

[9] El compuesto de [4] antes mencionado, en donde Z es $-CONR^aSO_2-$, o una de sus sales.

[10] El compuesto de [4] antes mencionado, en donde R^1 es

(1) un grupo alquilo de C_{1-10} o un grupo alquenilo de C_{2-10}, cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

un grupo alcoxi de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6};

un grupo carbamoilo opcionalmente mono- o disustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico aromático opcionalmente

sustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico no aromático opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

un grupo alcoxi de C_{1-6}-carbonilo;

un grupo carboxilo;

un grupo hidroxi;

un grupo ciano;

un grupo sililoxi opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo arilo de C_{6-14};

un grupo alquil de C_{1-6}-carboniloxi;

un grupo cicloalquiloxi de C_{3-10};

un grupo cicloalquil de C_{3-10}-alquiloxi de C_{1-6};

un grupo alquilsulfonilo de C_{1-6};

un grupo alquil de C_{1-6}-carbonilo; y

un grupo sulfamoiloxi;

(2) un grupo cicloalquilo de C_{3-10};

(3) un grupo arilo de C_{6-14};

(4) un grupo aralquilo de C_{7-13};

(5) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6};

(6) un grupo heterocíclico no aromático monocíclico; o

(7) un grupo heterocíclico aromático monocíclico, o una de sus sales.

[11] El compuesto de [4] antes mencionado, en donde R^2 es

(1) un átomo de hidrógeno;

(2) un grupo alquilo de C_{1-10} o un grupo alquenilo de C_{2-10}, cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6}; un átomo de halógeno; un grupo hidroxi; un grupo ciano; un grupo alquiltio de C_{1-6}; un grupo carbamoilo; un grupo ariloxi de C_{6-14}; un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquilo de C_{1-6}, un grupo alquil de C_{1-6}-carbonilo y un grupo arilo de C_{6-14}; un grupo heterocíclico aromático opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6}; y un grupo heterocíclico no aromático opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

(3) un grupo cicloalquilo de C_{3-10} opcionalmente sustituido con un grupo alquilo de C_{1-6} y opcionalmente condensado con un anillo benceno;

(4) un grupo arilo de C_{6-14} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un átomo de halógeno, un grupo nitro y un grupo ciano;

(5) un grupo aralquilo de C_{7-13} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo

alcoxi de C_{1-6} y un grupo arilo de C_{6-14};

(6) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6}; o

(7) un grupo heterocíclico no aromático opcionalmente sustituido con un grupo oxo, o una de sus sales.

[12] El compuesto de [4] antes mencionado, en donde el anillo A es un anillo benceno o un heterociclo aromático de 5 ó 6 miembros, o una de sus sales.

[13] El compuesto de [4] antes mencionado, en donde Y es un enlace, -O- o $-SO_2-$, o una de sus sales.

[14] El compuesto de [4] antes mencionado, en donde W es alquileno de C_{1-6} o alquenileno de C_{2-6}, o una de sus sales.

[15] El compuesto de [4] antes mencionado, que es

3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-(pentilsulfonil)propanamida,

(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida,

(pentilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo,

3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida,

3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida,

({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de butilo,

(2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}-N-(pentilsulfonil)acrilamida,

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo,

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo,

3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(pentilamino)sulfonil]propanamida,

(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]-N-(pentilsulfonil)acrilamida o

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxietoxi)fenil]propilo,

o una de sus sales.

[16] Un profármaco del compuesto de [4] antes mencionado o una de sus sales.

[17] Un agente farmacéutico que comprende el compuesto de [4] antes mencionado o una de sus sales o uno de sus profármacos.

[18] Un método para la prevención o el tratamiento de diabetes en un mamífero, que comprende la administración

del compuesto (I) o uno de sus profármacos al mamífero.

[19] Un método para mejorar la resistencia a la insulina en un mamífero, que comprende la administración del compuesto (I) o uno de sus profármacos al mamífero.

[20] Uso del compuesto (I) o uno de sus profármacos para la producción de un agente para la prevención o el tratamiento de diabetes.

[21] Uso del compuesto (I) o uno de sus profármacos para la producción de un sensibilizador de insulina.

De acuerdo con la presente invención, se puede proveer un agente para la prevención o el tratamiento de diabetes, que que está asociado con menor cantidad de efectos secundarios tales como aumento de peso corporal, acumulación de adipocitos, hipertrofia cardíaca y similares.

BREVE DESCRIPCION DE LAS FIGURAS

La Figura 1 muestra un patrón de difracción de polvos por rayos X de los cristales obtenidos en el Ejemplo 2.

La Figura 2 muestra un patrón de difracción de polvos por rayos X de los cristales obtenidos en el Ejemplo 12.

La Figura 3 muestra un patrón de difracción de polvos por rayos X de los cristales obtenidos en el Ejemplo 198.

La Figura 4 muestra un patrón de difracción de polvos por rayos X de los cristales obtenidos en el Ejemplo 204.

La Figura 5 muestra un patrón de difracción de polvos por rayos X de los cristales obtenidos en el Ejemplo 208.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La definición de cada símbolo en la fórmula (I) se describe en detalle a continuación.

En la presente especificación, el "átomo de halógeno" es un átomo de flúor, un átomo de cloro, un átomo de bromo o un átomo de yodo, salvo que se especifique otra cosa.

En la presente especificación, el "grupo alquilo de C_{1-6}" es metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo y similares, salvo que se especifique otra cosa.

En la presente especificación, el "grupo alcoxi de C_{1-6}" es metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, sec-butoxi, ter-butoxi y similares, salvo que se especifique otra cosa.

En la presente especificación, el "grupo alcoxi de C_{1-6}-carbonilo" es metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, ter-butoxicarbonilo y similares, salvo que se especifique otra cosa.

En la presente especificación, el "grupo alquil de C_{1-6}-carbonilo" es acetilo, propanoilo, butanoilo, isobutanoilo,

pentanoilo, isopentanoilo, hexanoilo y similares, salvo que se especifique otra cosa.

R^1 es un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido.

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido.

Como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 o R^2 se pueden mencionar, por ejemplo, un grupo alquilo de C_{1-10}, un grupo alquenilo de C_{2-10}, un grupo alquinilo de C_{2-10}, un grupo cicloalquilo de C_{3-10}, un grupo cicloalquenilo de C_{3-10}, un grupo cicloalcadienilo C_{4-10}, un grupo arilo de C_{6-14}, un grupo aralquilo de C_{7-13}, un grupo arilalquenilo de C_{8-13}, un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} y similares.

Como grupo alquilo de C_{1-10} se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo, heptilo, octilo, nonilo, decilo y similares.

Como grupo alquenilo de C_{2-10} se pueden mencionar, por ejemplo, etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo,

4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo, 1-heptenilo, 1-octenilo y similares.

Como grupo alquinilo de C_{2-10} se pueden mencionar, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, 1-heptinilo, 1-octinilo y similares.

Como grupo cicloalquilo de C_{3-10} se pueden mencionar, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, biciclo[2,2,1]heptilo, biciclo[2,2,2]octilo, biciclo[3,2,1]octilo, biciclo[3,2,2]nonilo, biciclo[3,3,1]nonilo, biciclo[4,2,1]nonilo, biciclo[4,3,1]decilo, adamantilo y similares.

Como grupo cicloalquenilo de C_{3-10} se pueden mencionar, por ejemplo, 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo y similares.

Como grupo cicloalcadienilo de C_{4-10} se pueden mencionar, por ejemplo, 2,4-ciclopentadien-1-ilo, 2,4-ciclohexadien-1-ilo, 2,5-ciclohexadien-1-ilo y similares.

El grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10} y cicloalcadienilo de C_{4-10} antes mencionados se puede condensar cada uno con un anillo benceno, y como tal grupo de anillo fusionado se pueden mencionar, por ejemplo, indanilo, dihidronaftilo, tetrahidronaftilo, fluorenilo y similares.

Además, también se pueden mencionar grupos hidrocarburos con enlaces cruzados tales como norbornanilo, adamantilo y similares como el grupo hidrocarburo antes mencionado.

Como grupo arilo de C_{6-14} se pueden mencionar, por ejemplo, fenilo, naftilo, antrilo, fenantrilo, acenaftilenilo, bifenililo y similares.

Como grupo aralquilo de C_{7-13} se pueden mencionar, por ejemplo, bencilo, fenetilo, fenilpropilo, naftilmetilo, bifenililmetilo y similares.

Como grupo arilalquenilo de C_{8-13} se pueden mencionar, por ejemplo, estirilo y similares.

Como grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} se pueden mencionar, por ejemplo, ciclopropilmetilo, ciclohexilmetilo y similares.

El grupo alquilo de C_{1-10}, grupo alquenilo de C_{2-10} y grupo alquinilo de C_{2-10} ejemplificados como el "grupo hidrocarburo" antes mencionado tienen opcionalmente 1 a 3 sustituyentes en posicion(es) sustituible(s).

Como tal sustituyente se pueden mencionar, por ejemplo,

(1) un grupo cicloalquilo de C_{3-10} (por ejemplo, ciclopropilo, ciclohexilo);

(2) un grupo arilo de C_{6-14} (por ejemplo, fenilo, naftilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente

sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un átomo de halógeno y un grupo aalquil de C_{1-6}-sulfoniloxi (por ejemplo, metilsulfoniloxi);

(3) un grupo heterocíclico aromático (por ejemplo, tienilo, furilo, piridilo, oxazolilo, tiazolilo, tetrazolilo, oxadiazolilo, pirazinilo, quinolilo, indolilo, imidazolilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6} y un átomo de halógeno;

(4) un grupo heterocíclico no aromático (por ejemplo, oxetanilo, tetrahidrofurilo, morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo, piperazinilo, dioxolilo, dioxolanilo, 1,3-dihidro-2-benzofuranilo, tiazolidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un grupo oxo y un átomo de halógeno;

(5) un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquilo de C_{1-6}, un grupo alquil de C_{1-6}-carbonilo, un grupo alcoxi de C_{1-6}-carbonilo, un grupo arilo de C_{6-14} (por ejemplo, fenilo), un grupo aril de C_{6-14}-carbonilo (por ejemplo, benzoilo), un grupo aralquil de C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo, fenetilcarbonilo), un grupo alquil de C_{1-6}-aminocarbonilo (por ejemplo,

metilaminocarbonilo, etilaminocarbonilo), un grupo aril de C_{6-14}-aminocarbonilo (por ejemplo, fenilaminocarbonilo, 1-naftilaminocarbonilo, 2-naftilaminocarbonilo), un grupo aralquil de C_{7-13}-aminocarbonilo (por ejemplo, bencilaminocarbonilo), un grupo alquilsulfonilo de C_{1-6} (por ejemplo, metilsulfonilo, etilsulfonilo, isopropilsulfonilo), un grupo arilsulfonilo de C_{6-14} (por ejemplo, bencensulfonilo, toluensulfonilo, 1-naftalensulfonilo, 2-naftalensulfonilo) y un grupo aralquilsulfonilo de C_{7-13} (por ejemplo, bencilsulfonilo);

(6) un grupo amidino;

(7) un grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(8) un grupo alcoxi de C_{1-6}-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(9) un grupo alquilsulfonilo de C_{1-6} (por ejemplo, metilsulfonilo) opcionalmente sustituido con 1 a 3 átomos de halógeno;

(10) un grupo carbamoilo opcionalmente mono- o disustituido con sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo arilo de C_{6-14} (por ejemplo, fenilo), un grupo aralquilo de C_{7-13} (por ejemplo, bencilo) y un grupo heterociclo-alquilo de C_{1-6} aromático (por ejemplo, furfurilo);

(11) un grupo tiocarbamoilo opcionalmente mono- o

disustituido con un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno;

(12) un grupo sulfamoilo opcionalmente mono- o disustituido con un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno;

(13) un grupo carboxilo;

(14) un grupo hidroxi;

(15) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo carboxilo, un grupo alcoxi de C_{1-6} y un grupo alcoxi de C_{1-6}-carbonilo;

(16) un grupo alqueniloxi de C_{2-6} (por ejemplo, eteniloxi) opcionalmente sustituido con 1 a 3 átomos de halógeno;

(17) un grupo cicloalquiloxi de C_{3-10} (por ejemplo, ciclopropiloxi, ciclohexiloxi);

(18) un grupo aralquiloxi de C_{7-13} (por ejemplo, benciloxi);

(19) un grupo ariloxi de C_{6-14} (por ejemplo, feniloxi, naftiloxi);

(20) un grupo alquil de C_{1-6}-carboniloxi (por ejemplo, acetiloxi, ter-butilcarboniloxi);

(21) un grupo mercapto;

(22) un grupo alquiltio de C_{1-6} (por ejemplo, metiltio, etiltio) opcionalmente sustituido con 1 a 3 átomos

de halógeno;

(23) un grupo aralquiltio de C_{7-13} (por ejemplo, benciltio);

(24) un grupo ariltio de C_{6-14} (por ejemplo, feniltio, naftiltio);

(25) un grupo sulfo;

(26) un grupo ciano;

(27) un grupo azido;

(28) un grupo nitro;

(29) un grupo nitroso;

(30) un átomo de halógeno;

(31) un grupo alquilsulfinilo de C_{1-6} (por ejemplo, metilsulfinilo);

(32) un grupo oxo;

(33) un grupo cicloalquil de C_{3-10}-alquil de C_{1-6}-oxi (por ejemplo, ciclopropilmetiloxi);

(34) un grupo alquilenodioxi C_{1-3} (por ejemplo, metilendioxi, etilendioxi);

(35) un grupo hidroxiimino opcionalmente sustituido con un grupo alquilo de C_{1-6};

(36) un grupo sililoxi opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo arilo de C_{6-14} (por ejemplo, triisopropilsililoxi, terbutil(difenil)sililoxi);

(37) un grupo aril de C_{6-14}-carbonilo (por ejemplo,

benzoilo) opcionalmente sustituido con 1 a 3 átomos de halógeno;

(38) un grupo sulfamoiloxi;

(39) un grupo carbamoiloxi;

y similares. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

El grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10}, grupo cicloalcadienilo de C_{4-10}, grupo arilo de C_{6-14}, grupo aralquilo de C_{7-13}, grupo arilalquenilo de C_{8-13} y grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} ejemplificados como el "grupo hidrocarburo" antes mencionado opcionalmente tienen 1 a 3 sustituyentes en posiciones sustituibles.

Como tal sustituyente, por ejemplo,

(1) los grupos ejemplificados como los sustituyentes que pueden opcionalmente tener el grupo alquilo de C_{1-10} antes mencionado y similares;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo carboxilo, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un grupo alcoxi de C_{1-6}-carbonilo, un grupo alquil de C_{1-6}-carboniloxi (por ejemplo, acetiloxi, ter-butilcarboniloxi), un grupo carbamoilo y un grupo heterocíclico no aromático (por ejemplo, piperidino);

(3) un grupo alquenilo de C_{2-6} (por ejemplo, etenilo, 1-propenilo) opcionalmente sustituido con 1 a 3 sustituyentes

seleccionados de un átomo de halógeno, un grupo carboxilo, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un grupo alcoxi de C_{1-6}-carbonilo y un grupo carbamoilo;

(4) un grupo aralquilo de C_{7-13} (por ejemplo, bencilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6} y un átomo de halógeno;

y similares. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^1 o R^2 se pueden mencionar un grupo heterocíclico aromático y un grupo heterocíclico no aromático.

En este caso, como grupo heterocíclico aromático se pueden mencionar, por ejemplo, un grupo heterocíclico aromático monocíclico de 4 a 7 miembros (de preferencia de 5 ó 6 miembros) que contiene, como un átomo constituyente además del átomo de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno, y un grupo heterocíclico aromático condensado. Como grupo heterocíclico aromático condensado se pueden mencionar, por ejemplo, un grupo en donde tal grupo heterocíclico aromático monocíclico de 4 a 7 miembros y uno o dos de un anillo de 5 ó 6 miembros que contienen 1 ó 2 átomos de nitrógeno, un anillo

de 5 miembros que contiene un átomo de azufre o un anillo benceno, y similares están condensados, y similares.

Los ejemplos preferidos del grupo heterocíclico aromático incluyen grupos heterocíclicos aromáticos monocíclicos tales como furilo (por ejemplo, 2-furilo, 3-furilo), tienilo (por ejemplo, 2-tienilo, 3-tienilo), piridilo (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo), pirimidinilo (por ejemplo, 2-pirimidinilo, 4-pirimidinilo, 5-pirimidinilo, 6-pirimidinilo), piridazinilo (por ejemplo, 3-piridazinilo, 4-piridazinilo), pirazinilo (por ejemplo, 2-pirazinilo), pirrolilo (por ejemplo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo), imidazolilo (por ejemplo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo), pirazolilo (por ejemplo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo), tiazolilo (por ejemplo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo), isotiazolilo (por ejemplo, 3-isotiazolilo, 4-isotiazolilo, 5-isotiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo), isoxazolilo (por ejemplo, 3-isoxazolilo, 4-isoxazolilo, 5-isoxazolilo), oxadiazolilo (por ejemplo, 1,2,4-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo), tiadiazolilo (por ejemplo, 1,3,4-tiadiazol-2-ilo), triazolilo (por ejemplo, 1,2,4-triazol-1-ilo, 1,2,4-triazol-3-ilo, 1,2,3-triazol-1-ilo, 1,2,3-triazol-2-ilo, 1,2,3-triazol-4-ilo), tetrazolilo (por ejemplo, tetrazol-1-ilo, tetrazol-5-ilo), triazinilo (por ejemplo, 1,2,4-triazin-1-ilo, 1,2,4-triazin-3-

il) y similares;

grupos heterocíclicos aromáticos condensados tales como quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo, 4-quinolilo, 6-quinolilo), isoquinolilo (por ejemplo, 3-isoquinolilo), quinazolilo (por ejemplo, 2-quinazolilo, 4-quinazolilo), quinoxalilo (por ejemplo, 2-quinoxalilo, 6-quinoxalilo), benzofurilo (por ejemplo, 2-benzofurilo, 3-benzofurilo), benzotienilo (por ejemplo, 2-benzotienilo, 3-benzotienilo), benzoxazolilo (por ejemplo, 2-benzoxazolilo), bencisooxazolilo (por ejemplo, 7-benzisooxazolilo), benzotiazolilo (por ejemplo, 2-benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol-1-ilo, bencimidazol-2-ilo, bencimidazol-5-ilo), benzotriazolilo (por ejemplo, 1H-1,2,3-benzotriazol-5-ilo), indolilo (por ejemplo, indol-1-ilo, indol-2-ilo, indol-3-ilo, indol-5-ilo), indazolilo (por ejemplo, 1H-indazol-3-ilo), pirrolopirazinilo (por ejemplo, 1H-pirrolo[2,3-b]pirazin-2-ilo, 1H-pirrolo[2,3-b]pirazin-6-ilo), imidazopiridinilo (por ejemplo, 1H-imidazo[4,5-b]piridin-2-ilo, 1H-imidazo[4,5-c]piridin-2-ilo, 2H-imidazo[1,2-a]piridin-3-ilo), imidazopirazinilo (por ejemplo, 1H-imidazo[4,5-b]pirazin-2-ilo), pirazolopiridinilo (por ejemplo, 1H-pirazolo[4,3-c]piridin-3-ilo), pirazolotienilo (por ejemplo, 2H-pirazolo[3,4-b]tiofen-2-ilo), pirazolotriazinilo (por ejemplo, pirazolo[5,1-c][1,2,4]triazin-3-il) y similares; y otros.

Como grupo heterocíclico no aromático se pueden mencionar, por ejemplo, un grupo heterocíclico no aromático monocíclico de 4 a 7 miembros (de preferencia, de 5 ó 6 miembros) que contiene, como un átomo constituyente además del átomo de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno, y un grupo heterocíclico no aromático condensado. Como grupo heterocíclico no aromático condensado se pueden mencionar, por ejemplo, un grupo en donde tal grupo heterocíclico no aromático monocíclico de 4 a 7 miembros y uno o dos de un anillo de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno, un anillo de 5 miembros que contiene un átomo de azufre o un anillo benceno, y similares están condensados, y otros.

Como ejemplos preferidos del grupo heterocíclico no aromático, se pueden mencionar grupos heterocíclicos no aromáticos monocíclicos tales como oxetanilo (por ejemplo, 2-oxetanilo, 3-oxetanilo), pirrolidinilo (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo), piperidinilo (por ejemplo, piperidino, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), morfolinilo (por ejemplo, morfolino), tiomorfolinilo (por ejemplo, tiomorfolino), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo, 3-piperazinilo), hexametileniminilo (por ejemplo, hexametilenimin-1-ilo), oxazolidinilo (por ejemplo, oxazolidin-2-ilo), tiazolidinilo

(por ejemplo, tiazolidin-2-ilo), imidazolidinilo (por ejemplo, imidazolidin-2-ilo, imidazolidin-3-ilo), oxazolinilo (por ejemplo, oxazolin-2-ilo), tiazolinilo (por ejemplo, tiazolin-2-ilo), imidazolinilo (por ejemplo, imidazolin-2-ilo, imidazolin-3-ilo), dioxolilo (por ejemplo, 1,3-dioxol-4-ilo), dioxolanilo (por ejemplo, 1,3-dioxolan-4-ilo), dihidrooxadiazolilo (por ejemplo, 4,5-dihidro-1,2,4-oxadiazol-3-ilo), 2-tioxo-1,3-oxazolidin-5-ilo, piranilo (por ejemplo, 4-piranilo), tetrahidropiranilo (por ejemplo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo), tiopiranilo (por ejemplo, 4-tiopiranilo), tetrahidrotiopiranilo (por ejemplo, 2-tetrahidrotiopiranilo, 3-tetrahidrotiopiranilo, 4-tetrahidrotiopiranilo), 1-oxidotetrahidrotiopiranilo (por ejemplo, 1-oxidotetrahidrotiopiran-4-ilo), 1,1-dioxidotetrahidrotiopiranilo (por ejemplo, 1,1-dioxidotetrahidrotiopiran-4-ilo), tetrahidrofurilo (por ejemplo, tetrahidrofurano-3-ilo, tetrahidrofurano-2-ilo), pirazolidinilo (por ejemplo, pirazolidin-1-ilo, pirazolidin-3-ilo), pirazolinilo (por ejemplo, pirazolin-1-ilo), tetrahidropirimidinilo (por ejemplo, tetrahidropirimidin-1-ilo), dihidrotriazolilo (por ejemplo, 2,3-dihidro-1H-1,2,3-triazol-1-ilo), tetrahidrotriazolilo (por ejemplo, 2,3,4,5-tetrahidro-1H-1,2,3-triazol-1-ilo), azepanilo (por ejemplo, azepan-3-ilo) y similares;

grupos heterocíclicos no aromáticos condensados tales como dihidroindolilo (por ejemplo, 2,3-dihidro-1H-isoindol-1-ilo), dihidroisoindolilo (por ejemplo, 1,3-dihidro-2H-isoindol-2-ilo), dihidrobenzofuranilo (por ejemplo, 2,3-dihidro-1-benzofuran-5-ilo), dihidrobenzodioxinilo (por ejemplo, 2,3-dihidro-1,4-benzodioxinilo), dihidrobenzodioxepinilo (por ejemplo, 3,4-dihidro-2H-1,5-benzodioxepinilo), tetrahidrobenzofuranilo (por ejemplo, 4,5,6,7-tetrahidro-1-benzofuran-3-ilo), cromenilo (por ejemplo, 4H-cromen-2-ilo, 2H-cromen-3-ilo), dihidroquinolinilo (por ejemplo, 1,2-dihidroquinolin-4-ilo), tetrahidroquinolinilo (por ejemplo, 1,2,3,4-tetrahidroquinolin-4-ilo), dihidroisoquinolinilo (por ejemplo, 1,2-dihidroisoquinolin-4-ilo), tetrahidroisoquinolinilo (por ejemplo, 1,2,3,4-tetrahidroisoquinolin-4-ilo), dihidroftalazinilo (por ejemplo, 1,4-dihidroftalazin-4-il) y similares; y otros.

El "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" antes mencionado tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como tal sustituyente se pueden mencionar, por ejemplo, los ejemplificados como los sustituyentes que pueden tener el grupo cicloalquilo de C_{3-10} y similares ejemplificado como el "grupo hidrocarburo" del grupo hidrocarburo "opcionalmente sustituido" antes mencionado. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o

diferentes.

R^1 es, de preferencia,

(1) un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, ter-butilo) o un grupo alquenilo de C_{2-10} (de preferencia, 3-butenilo), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

un grupo alcoxi de C_{1-6} (de preferencia, metoxi, etoxi) opcionalmente sustituido con un grupo alcoxi de C_{1-6} (de preferencia, metoxi);

un grupo carbamoilo opcionalmente mono- o disustituido con un grupo alquilo de C_{1-6} (de preferencia, dietilcarbamoilo);

un grupo heterocíclico aromático (de preferencia, piridilo, oxadiazolilo, furilo) opcionalmente sustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico no aromático (de preferencia, oxetanilo, pirrolidinilo, tetrahidrofurilo, dioxolanilo, morfolinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

un grupo alcoxi de C_{1-6}-carbonilo;

un grupo carboxilo;

un grupo hidroxi;

un grupo ciano;

un grupo sililoxi opcionalmente sustituido con 1 a 3

sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo arilo de C_{6-14} (de preferencia, ter-butil(difenil)sililoxi);

un grupo alquil de C_{1-6}-carboniloxi (de preferencia, acetiloxi);

un grupo cicloalquiloxi de C_{3-10} (de preferencia, ciclopropiloxi);

un grupo cicloalquil de C_{3-10}-alquil de C_{1-6}-oxi (de preferencia, ciclopropilmetiloxi);

un grupo alquilsulfonilo de C_{1-6} (de preferencia, metilsulfonilo);

un grupo alquil de C_{1-6}-carbonilo;

un grupo sulfamoiloxi;

y similares;

(2) un grupo cicloalquilo de C_{3-10} (de preferencia, ciclopropilo);

(3) un grupo arilo de C_{6-14} (de preferencia, fenilo);

(4) un grupo aralquilo de C_{7-13} (de preferencia, bencilo);

(5) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} (de preferencia, ciclopropilmetilo);

(6) un grupo heterocíclico no aromático monocíclico (de preferencia, tetrahidropiranilo);

(7) un grupo heterocíclico aromático monocíclico (de preferencia, pirimidinilo);

y similares.

R^1 es, con mayor preferencia,

un grupo alquilo de C_{1-10} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

un grupo alcoxi de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6}; y

un grupo hidroxi.

R^2 es, de preferencia,

(1) un átomo de hidrógeno;

(2) un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, isobutilo, ter-butilo, isobutilo, pentilo, isopentilo, neopentilo, hexilo) o un grupo alquenilo de C_{2-10} (de preferencia, propenilo), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6}; un átomo de halógeno; un grupo hidroxi; un grupo ciano; un grupo alquiltio de C_{1-6} (de preferencia, metiltio); un grupo carbamoilo; un grupo ariloxi de C_{6-14} (de preferencia, feniloxi); un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquilo de C_{1-6}, un grupo alquil de C_{1-6}-carbonilo y un grupo arilo de C_{6-14} (de preferencia, fenilo); un grupo heterocíclico aromático (de preferencia, tienilo, furilo, imidazolilo, piridilo, pirazinilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6}; y un grupo heterocíclico no aromático (de preferencia, tetrahidrofurilo, pirrolidinilo,

morfolinilo, tiomorfolinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

(3) un grupo cicloalquilo de C_{3-10} (de preferencia, ciclohexilo, ciclobutilo, cicloheptilo, indanilo, tetrahidronaftilo) opcionalmente sustituido con un grupo alquilo de C_{1-6} y opcionalmente condensado con un anillo benceno;

(4) un grupo arilo de C_{6-14} (de preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un átomo de halógeno, un grupo nitro, un grupo ciano y similares;

(5) un grupo aralquilo de C_{7-13} (de preferencia, bencilo, fenetilo, fenilpropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6} y un grupo arilo de C_{6-14} (de preferencia, fenilo);

(6) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} (de preferencia, ciclopropilmetilo);

(7) un grupo heterocíclico no aromático (de preferencia, azepanilo) opcionalmente sustituido con un grupo oxo;

y similares.

R^2 es, con mayor preferencia,

un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, isobutilo, ter-butilo, isobutilo, pentilo, isopentilo, neopentilo, hexilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6}; un átomo de halógeno; un grupo hidroxi; un grupo ciano; un grupo alquiltio de C_{1-6} (de preferencia, metiltio); un grupo carbamoilo; un grupo ariloxi de C_{6-14} (de preferencia, feniloxi); un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquilo de C_{1-6}, un grupo alquil de C_{1-6}-carbonilo y un grupo arilo de C_{6-14} (de preferencia, fenilo); un grupo heterocíclico aromático (de preferencia, tienilo, furilo, imidazolilo, piridilo, pirazinilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6}; y un grupo heterocíclico no aromático (de preferencia, tetrahidrofurilo, pirrolidinilo, morfolinilo, tiomorfolinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo.

El anillo A es un anillo aromático que está además opcionalmente sustituido. Como "anillo aromático" se pueden mencionar, por ejemplo, hidrocarburo aromático, heterociclo aromático, y similares. Como hidrocarburo aromático se pueden mencionar, por ejemplo, un areno C_{6-14} y similares. Como el areno C_{6-14}, se pueden mencionar un anillo que constituye el

grupo arilo de C_{6-14} ejemplificado como R^1 o R^2 antes mencionados. Como heterociclo aromático se puede mencionar un anillo que constituye el grupo heterocíclico aromático ejemplificado como R^1 o R^2 antes mencionados. El anillo aromático es, de preferencia, un anillo benceno, un heterociclo aromático de 5 ó 6 miembros (de preferencia, pirazol, pirrol) y similares.

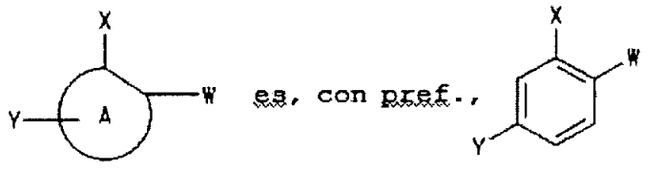
El "anillo aromático" para el anillo A está sustituido con un grupo -X-, un grupo -Y- y un grupo -W-, y opcionalmente tiene también 1 a 3 sustituyentes en posiciones sustituibles. Como tal sustituyente se pueden mencionar aquellos ejemplificados como los sustituyentes que puede tener el grupo cicloalquilo de C_{3-10} y similares ejemplificado para R^1 o R^2 antes mencionados. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes. El sustituyente es, de preferencia, un grupo alquilo de C_{1-6}.

En la fórmula (I), el grupo -X- y el grupo -W- significan sustitución en la posición orto del anillo A.

El anillo A es, de preferencia, un anillo benceno o un heterociclo aromático de 5 ó 6 miembros (de preferencia, pirazol, pirrol; con mayor preferencia, pirazol), cada uno opcionalmente sustituido con un grupo alquilo de C_{1-6}, y similares, con mayor preferencia, un anillo benceno o un heterociclo aromático de 5 ó 6 miembros (de preferencia, pirazol, pirrol; con mayor preferencia, pirazol).

Cuando, en la fórmula (I), el anillo A es un anillo

benceno o un anillo pirazol, una fórmula estructural parcial



Ar es "un anillo monocíclico opcionalmente sustituido". Aquí, el "anillo monocíclico" incluye un "anillo aromático monocíclico" y un "anillo no aromático monocíclico". Como "anillo aromático monocíclico", se pueden mencionar anillos monocíclicos de entre los hidrocarburos aromáticos y heterociclos aromáticos ejemplificados como el anillo A antes mencionado. El anillo aromático monocíclico es, de preferencia, un anillo benceno, un heterociclo aromático monocíclico de 5 ó 6 miembros (de preferencia, piridina, piridazina, oxazol, tiazol) y similares. Como el "anillo no aromático monocíclico", se pueden mencionar cicloalcano de C_{3-10}, cicloalqueno de C_{3-10} y cicloalcadieno de C_{4-10} correspondiente al grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} ejemplificado como R^1 o R^2 antes mencionados, y un heterociclo no aromático monocíclico correspondiente al grupo heterocíclico no aromático monocíclico ejemplificado como R^1 o R^2 antes mencionado (específicamente, un heterociclo no aromático monocíclico de 5 ó 6 miembros que contiene, como un átomo constituyente además del átomo de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno; de preferencia, piperidina,

tetrahidrofurano). El anillo no aromático monocíclico es, de preferencia, un cicloalcano de C_{3-10} (de preferencia, ciclopropano, ciclohexano), un heterociclo no aromático monocíclico de 5 ó 6 miembros (de preferencia, piperidina, tetrahidrofurano) y similares.

Ar es, de preferencia, un anillo aromático monocíclico opcionalmente sustituido, con mayor preferencia, un "heterociclo aromático monocíclico opcionalmente sustituido de 5 ó 6 miembros (de preferencia, piridina, piridazina, oxazol, tiazol; con mayor preferencia, piridina)" o un "anillo benceno sustituido".

El anillo monocíclico (anillo aromático monocíclico y anillo no aromático monocíclico) para Ar tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como dicho sustituyente, se pueden mencionar aquellos ejemplificados como los sustituyentes que puede tener el grupo cicloalquilo de C_{3-10} y similares ejemplificado como R^1 o R^2 antes mencionados.

El sustituyente de Ar es, de preferencia,

(1) un átomo de halógeno;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno (de preferencia, metilo, trifluorometilo);

(3) un grupo arilo de C_{6-14} (de preferencia, fenilo);

(4) un grupo nitro;

(5) un grupo carboxilo;

(6) un grupo alquil de C_{1-6}-carbonilo (de preferencia, acetilo);

(7) un grupo alcoxi de C_{1-6}-carbonilo (de preferencia, etoxicarbonilo, ter-butoxicarbonilo);

(8) un grupo aril de C_{6-14}-carbonilo (de preferencia, benzoilo);

(9) un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquil de C_{1-6}-carbonilo (de preferencia, acetilo), un grupo alcoxi de C_{1-6}-carbonilo (de preferencia, etoxicarbonilo, ter-butoxicarbonilo) y alquilsulfonilo de C_{1-6} (de preferencia, metilsulfonilo), y similares.

Cuando el anillo aromático monocíclico para Ar es un anillo benceno, Ar es, de preferencia, un anillo benceno sustituido.

Ar es, de preferencia,

un anillo benceno, un heterociclo aromático monocíclico de 5 ó 6 miembros (de preferencia, piridina, piridazina, oxazol, tiazol), un cicloalcano de C_{3-10} (de preferencia, ciclopropano, ciclohexano) y un heterociclo no aromático monocíclico de 5 ó 6 miembros (de preferencia, piperidina, tetrahidrofurano), cada uno opcionalmente con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido

con 1 a 3 átomos de halógeno (de preferencia, metilo, trifluorometilo);

(3) un grupo arilo de C_{6-14} (de preferencia, fenilo);

(4) un grupo nitro;

(5) un grupo carboxilo;

(6) un grupo alquil de C_{1-6}-carbonilo (de preferencia, acetilo);

(7) un grupo alcoxi de C_{1-6}-carbonilo (de preferencia, etoxicarbonilo, ter-butoxicarbonilo);

(8) un grupo aril de C_{6-14}-carbonilo (de preferencia, benzoilo);

(9) un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquil de C_{1-6}-carbonilo (de preferencia, acetilo), un grupo alcoxi de C_{1-6}-carbonilo (de preferencia, etoxicarbonilo, ter-butoxicarbonilo) y un grupo alquilsulfonilo de C_{1-6} (de preferencia, metilsulfonilo);

y similares.

Ar es, con mayor preferencia,

un anillo benceno o un heterociclo aromático monocíclico de 5 ó 6 miembros (de preferencia, piridina) opcionalmente con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno (de preferencia, metilo,

trifluorometilo);

y similares.

X es un espaciador que tiene una cadena principal de 1 ó 2 átomos.

Tal como se usa en la presente, la "cadena principal" es una cadena lineal divalente que conecta el anillo A y el anillo Ar, y el número de átomos de la cadena principal se cuenta de modo que la cantidad de átomos en la cadena principal es mínima. La "cadena principal" consiste en 1 ó 2 átomos seleccionados de un átomo de carbono y un heteroátomo (por ejemplo, átomo de oxígeno, átomo de azufre, átomo de nitrógeno y similares), y puede ser saturada o insaturada. El átomo de azufre puede estar oxidado.

Y es un enlace o un espaciador con una cadena principal de 1 ó 2 átomos.

Tal como se usa en la presente, la "cadena principal" es una cadena lineal divalente que conecta el anillo A y el grupo $-R^1$, y el número de átomos de la cadena principal se cuenta de modo que la cantidad de átomos en la cadena principal es mínima. La "cadena principal" consiste en 1 ó 2 átomos seleccionados de un átomo de carbono y un heteroátomo (por ejemplo, átomo de oxígeno, átomo de azufre, átomo de nitrógeno y similares), y puede ser saturada o insaturada. El átomo de azufre puede estar oxidado.

En el "espaciador que tiene una cadena principal de

1 ó 2 átomos" para X o Y, el átomo de carbono y el átomo de nitrógeno que constituyen la cadena principal tienen opcionalmente uno o varios sustituyentes en posiciones sustituibles. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como el "sustituyente", se pueden mencionar aquellos ejemplificados como los sustituyentes que pueden tener el grupo cicloalquilo de C_{3-10} y similares ejemplificado como R^1 o R^2 antes mencionados.

Ejemplos específicos del "espaciador que tiene una cadena principal de 1 ó 2 átomos" para X o Y incluyen

(1) $-(CH_2)_k-$, en donde k es 1 ó 2 (de preferencia, $-CH_2-$, $-CH_2CH_2-$),

(2) $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1 (de preferencia, -O-, $-OCH_2-$, $-CH_2O-$),

(3) $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$, en donde uno de k21 y k22 es 0 y el otro es 0 ó 1, y k23 es un número entero de 0 a 3 (de preferencia, -S-, $-SO_2-$, $-SCH_2-$, $-CH_2S-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-SO_3-$),

(4) $-(CH_2)_{k31}-NH-(CH_2)_{k32}-$, en donde uno de k31 y k32 es 0 y el otro es 0 ó 1 (de preferencia, -NH-, $-NHCH_2-$, $-CH_2NH-$) y similares, cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo oxo, un grupo alquilo de C_{1-6}, etc.

X es, de preferencia, $-(CH_2)_k-$, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, -

$(CH_2)_{k31}$-NH-$(CH_2)_{k32}$- y similares, cada uno opcionalmente sustituido con un grupo oxo, con mayor preferencia, $-CH_2-$, -O-, $-CH_2O-$, -NH-, -CO-NH- y similares, de preferencia particular, $-CH_2-$ y -O-. X es, de preferencia particular, -O- (átomo de oxígeno).

En particular, cuando Ar es un "heterociclo aromático monocíclico opcionalmente sustituido de 5 ó 6 miembros (de preferencia, piridina)", X es, de preferencia, -O-.

Cuando Ar es un "anillo benceno opcionalmente sustituido (de preferencia, anillo benceno sustituido)", X es, de preferencia, $-CH_2-$.

Y es, de preferencia, un enlace, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$ y similares, con mayor preferencia, un enlace, -O-, $-SO_2-$, $-SO_3-$ ($-O-SO_2-$ o $-SO_2-O-$) y similares, de preferencia particular, un enlace, -O- o $-SO_2-$. En particular, se prefiere -O-.

Como "grupo hidrocarburo divalente con 1 a 20 átomos de carbono" para W se pueden mencionar, por ejemplo, un "grupo hidrocarburo divalente acíclico", un "grupo hidrocarburo divalente cíclico" o un grupo divalente obtenido por combinación de uno o varios tipos de "grupos hidrocarburos divalentes acíclicos" y uno o varios tipos de "grupos hidrocarburos divalentes cíclicos".

Aquí, como el "grupo hidrocarburo divalente

acíclico" se pueden mencionar, por ejemplo, alquileno con 1 a 20 átomos de carbono, alquenileno con 2 a 20 átomos de carbono, alquinileno con 2 a 20 átomos de carbono y similares.

Como el "grupo hidrocarburo divalente cíclico", se pueden mencionar un grupo divalente y similar obtenido por eliminación de cualquiera de los dos átomos de hidrógeno del cicloalcano con 5 a 20 átomos de carbono, cicloalqueno con 5 a 20 átomos de carbono o hidrocarburo aromático con 6 a 18 átomos de carbono (por ejemplo, benceno, naftaleno, indeno, antraceno). Los ejemplos específicos incluyen 1,2-ciclopentileno, 1,3-ciclopentileno, 1,2-ciclohexileno, 1,3-ciclohexileno, 1,4-ciclohexileno, 1,2-cicloheptileno, 1,3-cicloheptileno, 1,4-cicloheptileno, 3-ciclohexen-1,4-ileno, 3-ciclohexen-1,2-ileno, 2,5-ciclohexadien-1,4-ileno, 1,2-fenileno, 1,3-fenileno, 1,4-fenileno, 1,4-naftileno, 1,6-naftileno, 2,6-naftileno, 2,7-naftileno, 1,5-indenileno, 2,5-indenileno, y similares.

El "grupo hidrocarburo divalente con 1 a 20 átomos de carbono" es, de preferencia, un grupo hidrocarburo divalente con 1 a 6 átomos de carbono, y se prefieren en especial

(1) alquileno de C_{1-6} (por ejemplo, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-(CH_2)_2CH(CH_3)-$, $-CH_2-CH(CH_3)-CH_2-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, $-CH_2-CH(CH_3)-$,

$-CH_2-C(CH_3)_2-$);

(2) alquenileno de C_{2-6} (por ejemplo, $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, $-CH=C(CH_3)-$, $-CH=C(C_2H_5)-$);

(3) alquinileno de C_{2-6} (por ejemplo, $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$) y similares.

El "grupo hidrocarburo divalente con 1 a 20 átomos de carbono" para W tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como tal sustituyente se pueden mencionar, por ejemplo,

(1) un átomo de halógeno,

(2) un grupo hidroxi,

(3) un grupo ciano,

(4) un grupo nitro,

(5) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno,

(6) un grupo alquiltio de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno,

y similares.

W es, de preferencia, alquileno de C_{1-6} o alquenileno de C_{2-6}, cada uno opcionalmente sustituido con un grupo alcoxi de C_{1-6}, con mayor preferencia, alquileno de C_{1-6} (de preferencia, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2-CH(CH_3)-$ o $-CH_2-C(CH_3)_2-$; con mayor preferencia, $-(CH_2)_2-$ o $-(CH_2)_3-$) o alquenileno de C_{2-6} (de

preferencia, -CH=CH-, -CH=CH-CH_2-, -CH=C(CH_3)- o -CH=C(C_2H_5)-; con mayor preferencia, -CH=CH-). En particular, se prefieren -$(CH_2)_2$-, -$(CH_2)_3$- y -CH=CH-.

Z es -$CONR^aSO_2$-, -SO_2NR^aCO-, -SO_2NR^aCOO-, -NR^aSO_2-, -$OCONR^aSO_2$-, -$OCONR^aSO_2NR^c$-, -$OCONR^c$-, -$NR^aCONR^bSO_2$-, -$NR^aSO_2NR^bCOO$- o -$CONR^aSO_2NR^c$-.

Aquí, "Ra" y "Rb" son cada uno, de manera independiente, un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, "Rc" es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, o Rc y R2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo opcionalmente sustituido con contenido de nitrógeno".

Como el "grupo hidrocarburo opcionalmente sustituido" para R^a, R^b o R^c, se pueden mencionar aquellos ejemplificados como R^1 o R^2 antes mencionados.

De ellos, se prefiere un grupo alquilo de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6}.

Como "grupo protector amino" para R^a, R^b o R^c, se pueden mencionar, por ejemplo, formilo, un grupo alquil de C_{1-6}-carbonilo, un grupo alcoxi de C_{1-6}-carbonilo, un grupo benzoilo, un grupo aralquil de C_{7-10}-carbonilo (por ejemplo, bencilcarbonilo), un grupo aralquiloxi de C_{7-14}-carbonilo (por ejemplo, benciloxicarbonilo, 9-fluorenilmetoxicarbonilo), un

grupo ftaloilo, un grupo sililo sustituido (por ejemplo, un grupo tri-alquil de C_{1-6}-sililo tales como trimetilsililo, trietilsililo, ter-butildimetilsililo y ter-butildietilsililo; ter-butildifenilsililo) y similares. Estos grupos están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo alcoxi de C_{1-6} y un grupo nitro.

Como el "heterociclo que contiene nitrógeno" del "heterociclo que contiene nitrógeno opcionalmente sustituido" formado, junto con el átomo de nitrógeno adyacente, por R^c y R^2 unidos entre sí, se pueden mencionar, por ejemplo, un heterociclo que contiene nitrógeno de 5 a 7 miembros que tiene, como un átomo constituyente además del átomo de carbono, al menos un átomo de nitrógeno, y además, 1 ó 2 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno, que está opcionalmente condensado con un anillo benceno. Los ejemplos preferidos del heterociclo que contiene nitrógeno incluyen pirrolidina, imidazolidina, pirazolidina, piperidina, piperazina, morfolina, tiomorfolina, oxopiperazina, oxopirrolidina y dihidroisoindolina.

El heterociclo que contiene nitrógeno tiene opcionalmente 1 a 3 (de preferencia, 1 ó 2) sustituyentes en posiciones sustituibles. Como dicho sustituyente, se pueden mencionar aquellos ejemplificados como los sustituyentes que pueden tener el grupo cicloalquilo de C_{3-10} y similares

ejemplificado como R^1 o R^2 antes mencionados. En particular, se prefieren un grupo alquilo de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6}, un grupo carbamoilo y similares. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

R^a y R^b son cada uno, de preferencia, de modo independiente, un átomo de hidrógeno o un grupo alquilo de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6}, con mayor preferencia, un átomo de hidrógeno.

R^c es, de preferencia, un átomo de hidrógeno o un grupo alquilo de C_{1-6}, o R^c y R^2 están enlazados entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo que contiene nitrógeno (de preferencia, morfolina, pirrolidina, piperidina, piperazina, tiomorfolina, oxopirrolidina, dihidroisoindolina) que opcionalmente tiene 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6} y un grupo carbamoilo.

Z es de preferencia, $-CONR^aSO_2-$, $-SO_2NR^aCOO-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$ o $-CONR^aSO_2NR^c-$, con mayor preferencia, $-CONR^aSO_2-$ y similares. Z es de preferencia particular, $-CONHSO_2-$.

De los compuestos (I), los compuestos en donde Ar no es un anillo benceno no sustituido, que son distintos de los siguientes compuestos, son nuevos.

ácido (4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acético,

(4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acetato de etilo,

[4-(dietilamino)-2-metilfenil]carbamato de 1-{4-metoxi-2-[(4-vinilbencil)oxi]fenil}etilo,

N-{2-[4,5-dimetoxi-2-(2-tienilcarbonil)fenil]etil}-N,4-dimetilbencensulfonamida,

N-(2,2-dimetoxietil)-N-{3-[6-({(2,2-dimetoxietil)[(4-metilfenil)sulfonil]amino}metil)-2,3-dimetoxifenoxi]-4-metoxibencil}-4-metilbencensulfonamida, y

fenilcarbamato de 2-[2-(3,4-dimetoxifenil)etil]-4,5-dimetoxibencilo.

Los ejemplos preferidos de compuesto (I) incluyen los siguientes compuestos.

[Compuesto AA]

El compuesto (I), en donde

el anillo A es un anillo benceno, un heterociclo aromático de 5 ó 6 miembros, etc. (de preferencia, pirazol, pirrol, con mayor preferencia, pirazol), cada uno opcionalmente sustituido con un grupo alquilo de C_{1-6};

Ar es un anillo benceno, un heterociclo aromático monocíclico de 5 ó 6 miembros (de preferencia, piridina, piridazina, oxazol, tiazol), un cicloalcano C_{3-10} (de preferencia, ciclopropano, ciclohexano) y un heterociclo no

aromático monocíclico de 5 ó 6 miembros (de preferencia, piperidina, tetrahidrofurano), cada uno opcionalmente con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno (de preferencia, metilo, trifluorometilo);

(3) un grupo arilo de C_{6-14} (de preferencia, fenilo);

(4) un grupo nitro;

(5) un grupo carboxilo;

(6) un grupo alquil de C_{1-6}-carbonilo (de preferencia, acetilo);

(7) un grupo alcoxi de C_{1-6}-carbonilo (de preferencia, etoxicarbonilo, ter-butoxicarbonilo);

(8) un grupo aril de C_{6-14}-carbonilo (de preferencia, benzoilo);

(9) un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquil de C_{1-6}-carbonilo (de preferencia, acetilo), un grupo alcoxi de C_{1-6}-carbonilo (de preferencia, etoxicarbonilo, ter-butoxicarbonilo) y un grupo alquilsulfonilo de C1-6 (de preferencia, metilsulfonilo);

y similares;

R^1 es (1) un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, ter-butilo) o un

grupo alquenilo de C_{2-10} (de preferencia, 3-butenilo), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

un grupo alcoxi de C_{1-6} (de preferencia, metoxi, etoxi) opcionalmente sustituido con un grupo alcoxi de C_{1-6} (de preferencia, metoxi);

un grupo carbamoilo opcionalmente mono- o disustituido con un grupo alquilo de C_{1-6} (de preferencia, dietilcarbamoilo);

un grupo heterocíclico aromático (de preferencia, piridilo, oxadiazolilo, furilo) opcionalmente sustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico no aromático (de preferencia, oxetanilo, pirrolidinilo, tetrahidrofurilo, dioxolanilo, morfolinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

un grupo alcoxi de C_{1-6}-carbonilo;

un grupo carboxilo;

un grupo hidroxi;

un grupo ciano;

un grupo sililoxi opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo arilo de C_{6-14} (de preferencia, ter-butil(difenil)sililoxi);

un grupo alquil de C_{1-6}-carboniloxi (de preferencia,

acetiloxi);

un grupo cicloalquiloxi de C_{3-10} (de preferencia, ciclopropiloxi);

un grupo cicloalquil de C_{3-10}-alquiloxi de C_{1-6} (de preferencia, ciclopropilmetiloxi);

un grupo alquilsulfonilo de C_{1-6} (de preferencia, metilsulfonilo);

un grupo alquil de C_{1-6}-carbonilo; y

un grupo sulfamoiloxi;

(2) un grupo cicloalquilo de C_{3-10} (de preferencia, ciclopropilo);

(3) un grupo arilo de C_{6-14} (de preferencia, fenilo);

(4) un grupo aralquilo de C_{7-13} (de preferencia, bencilo);

(5) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} (de preferencia, ciclopropilmetilo);

(6) un grupo heterocíclico no aromático monocíclico (de preferencia, tetrahidropiranilo); o

(7) un grupo heterocíclico aromático monocíclico (de preferencia, pirimidinilo);

R^2 es

(1) un átomo de hidrógeno;

(2) un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, isobutilo, ter-butilo, isobutilo, pentilo, isopentilo, neopentilo, hexilo) o un grupo

alquenilo de C_{2-10} (de preferencia, propenilo), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6}; un átomo de halógeno; un grupo hidroxi; un grupo ciano; un grupo alquiltio de C_{1-6} (de preferencia, metiltio); un grupo carbamoilo; un grupo ariloxi de C_{6-14} (de preferencia, feniloxi); un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquilo de C_{1-6}, un grupo alquil de C_{1-6}-carbonilo y un grupo arilo de C_{6-14} (de preferencia, fenilo); un grupo heterocíclico aromático (de preferencia, tienilo, furilo, imidazolilo, piridilo, pirazinilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6}; y un grupo heterocíclico no aromático (de preferencia, tetrahidrofurilo, pirrolidinilo, morfolinilo, tiomorfolinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

(3) un grupo cicloalquilo de C_{3-10} (de preferencia, ciclohexilo, ciclobutilo, cicloheptilo, indanilo, tetrahidronaftilo) opcionalmente sustituido con un grupo alquilo de C_{1-6} y opcionalmente condensado con un anillo benceno;

(4) un grupo arilo de C_{6-14} (de preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6},

un átomo de halógeno, un grupo nitro, un grupo ciano, etc.;

(5) un grupo aralquilo de C_{7-13} (de preferencia, bencilo, fenetilo, fenilpropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6} y un grupo arilo de C_{6-14} (de preferencia, fenilo);

(6) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} (de preferencia, ciclopropilmetilo); o

(7) un grupo heterocíclico no aromático (de preferencia, azepanilo) opcionalmente sustituido con un grupo oxo;

X es $-(CH_2)_k-$, en donde k es 1 ó 2, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1, o $-(CH_2)_{k31}-NH-(CH_2)_{k32}-$, en donde uno de k31 y k32 es 0 y el otro es 0 ó 1, cada uno opcionalmente sustituido con un grupo oxo;

Y es un enlace, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1, o $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$, en donde uno de k21 y k22 es 0 y el otro es 0 ó 1, k23 es un número entero de 0 a 3;

W es un alquileno de C_{1-6} o un alquenileno de C_{2-6}, cada uno opcionalmente sustituido con un grupo alcoxi de C_{1-6};

Z es $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$, $-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$ o $-CONR^aSO_2NR^c-$;

R^a y R^b son cada uno, de manera independiente, un átomo de hidrógeno o un grupo alquilo de C_{1-6} opcionalmente

sustituido con un grupo alcoxi de C_{1-6}; y

R^c es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, o R^c y R^2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo que contiene nitrógeno (de preferencia, morfolina, pirrolidina, piperidina, piperazina, tiomorfolina, oxopirrolidina, dihidroisoindolina) opcionalmente con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6} y un grupo carbamoilo.

[Compuesto A]

El compuesto (I), en donde

el anillo A es un anillo benceno, un heterociclo aromático de 5 ó 6 miembros, etc. (de preferencia, pirazol);

Ar es un anillo benceno o un heterociclo aromático monocíclico de 5 ó 6 miembros (de preferencia, piridina), cada uno opcionalmente con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno (de preferencia, metilo, trifluorometilo);

y similares;

R^1 es

(1) un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, ter-butilo) opcionalmente sustituido con un sustituyente seleccionado de

un grupo alcoxi de C_{1-6} (de preferencia, metoxi);

un grupo carbamoilo (de preferencia, dietilcarbamoilo) opcionalmente mono- o disustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico aromático (de preferencia, piridilo, oxadiazolilo) opcionalmente sustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico no aromático (de preferencia, oxetanilo, pirrolidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

un grupo alcoxi de C_{1-6}-carbonilo;

un grupo carboxilo;

etc.;

(2) un grupo cicloalquilo de C_{3-10} (de preferencia, ciclopropilo);

(3) un grupo arilo de C_{6-14} (de preferencia, fenilo);

(4) un grupo aralquilo de C_{7-13} (de preferencia, bencilo);

(5) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} (de preferencia, ciclopropilmetilo); o

(6) un grupo heterocíclico no aromático monocíclico (de preferencia, tetrahidropiranilo);

R^2 es

(1) un átomo de hidrógeno;

(2) un grupo alquilo de C_{1-10} (de preferencia, metilo, etilo, propilo, isopropilo, butilo, isobutilo, ter-butilo, isobutilo, pentilo, isopentilo, neopentilo, hexilo) o un grupo alquenilo de C_{2-10} (de preferencia, propenilo), cada uno opcionalmente sustituido con un grupo alcoxi de C_{1-6};

(3) un grupo cicloalquilo de C_{3-10} (de preferencia, ciclohexilo);

(4) un grupo arilo de C_{6-14} (de preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un átomo de halógeno, un grupo nitro, etc.;

(5) un grupo aralquilo de C_{7-13} (de preferencia, bencilo, fenilpropilo); o

(6) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} (de preferencia, ciclopropilmetilo);

X es $-(CH_2)_k-$, en donde k es 1 ó 2 o $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1;

Y es un enlace, $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1, o $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$, en donde uno de k21 y k22 es 0 y el otro es 0 ó 1, y k23 es un número entero de 0 a 3;

W es alquileno de C_{1-6} o alquenileno de C_{2-6};

Z es -CONRaSO2-, -SO2NRaCO-, -SO2NRaCOO-, -NRaSO2-, -OCONRaSO2-, -OCONRaSO2NRc-, -OCONRc-, -NRaCONRbSO2- o

-CONRaSO2NRc-;

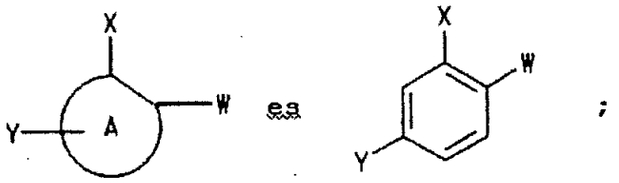
R^a y R^b son átomos de hidrógeno; y

R^c es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, o R^c y R^2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo que contiene nitrógeno (de preferencia, morfolina).

[Compuesto B]

El compuesto (I), en donde

el anillo A es un anillo benceno;



X es $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1;

Y es $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1, o $-(CH_2)_{k21}-S(O)_{k23}-(CH_2)_{k22}-$, en donde uno de k21 y k22 es 0 y el otro es 0 ó 1 y k23 es un número entero de 0 a 3;

Z es -CONRaSO2-, -NRaSO2-, -OCONRaSO2-, -OCONRaSO2NRc-, -OCONRc- o -CONRaSO2NRc-;

R^a es un átomo de hidrógeno;

R^c es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, o R^c y R^2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo que contiene nitrógeno (de preferencia, morfolina); y

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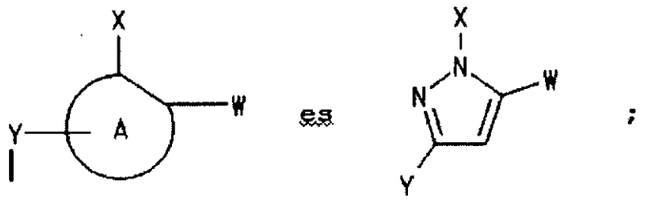
Ar, R^1, R^2 y W son como se definen en el [compuesto A] antes mencionado.

[Compuesto C]

El compuesto (I) en donde

el anillo A es pirazol;



;

X es $-(CH_2)_k-$, en donde k es 1 ó 2;

Y es un enlace o $-(CH_2)_{k11}-O-(CH_2)_{k12}-$, en donde uno de k11 y k12 es 0 y el otro es 0 ó 1;

Z es $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-OCONR^aSO_2-$ o $-NR^aCONR^bSO_2-$;

R^a y R^b son átomos de hidrógeno; y

Ar, R^1, R^2 y W son como se definen en el [compuesto A] antes mencionado.

[Compuesto D]

El compuesto (I) que es

3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-(pentilsulfonil)propanamida (Ejemplo 2),

(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (Ejemplo 12),

(pentilsulfonil)carbamato de 3-[2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (Ejemplo 28),

3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (Ejemplo 97),

3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (Ejemplo 122),

({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de butilo (Ejemplo 129),

(2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}-N-(pentilsulfonil)acrilamida (Ejemplo 198),

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (Ejemplo 204),

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (Ejemplo 208),

3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(pentilamino)sulfonil]propanamida (Ejemplo 214),

(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]-N-(pentilsulfonil)acrilamida (Ejemplo 250), o

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

hidroxietoxi)fenil]propilo (Ejemplo 439).

Las sales con el compuesto representado por la fórmula (I) son, de preferencia, sales farmacéuticamente aceptables y, por ejemplo, se pueden mencionar sales con bases inorgánicas, sales con bases orgánicas, sales con ácidos inorgánicos, sales con ácidos orgánicos, sales con aminoácidos básicos o ácidos, y similares.

Los ejemplos preferidos de las sales con base inorgánica incluyen sales de metales alcalinos tales como sal de sodio, sal de potasio y similares; sales de metales alcalinotérreos tales como sal de calcio, sal de magnesio y similares; sal de aluminio, sal de amonio y similares.

Los ejemplos preferidos de la sal con base orgánica incluyen una sal con trimetilamina, trietilamina, piridina, picolina, etanolamina, dietanolamina, trietanolamina, trometamin[tris(hidroximetil)metilamina], ter-butilamina, ciclohexilamina, bencilamina, diciclohexilamina, N,N'-dibenciletilenodiamina y similares.

Los ejemplos preferidos de la sal con ácido inorgánico incluyen una sal con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, y similares.

Los ejemplos preferidos de la sal con ácido orgánico incluyen una sal con ácido fórmico, ácido acético, ácido trifluoroacético, ácido ftálico, ácido fumárico, ácido oxálico,

ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido málico, ácido metansulfónico, ácido bencensulfónico, ácido p-toluensulfónico, y similares.

Los ejemplos preferidos de la sal don aminoácido básico incluyen una sal con arginina, lisina, ornitina y similares.

Los ejemplos preferidos de la sal con aminoácido ácido incluyen una sal con ácido aspártico, ácido glutámico, y similares.

El profármaco del compuesto (I) es un compuesto que se convierte en el compuesto (I) con una reacción debida a una enzima, ácido gástrico, etc. en la condición fisiológica en el organismo vivo, es decir, un compuesto que se convierte en el compuesto (I) por oxidación enzimática, reducción, hidrólisis, etc.; un compuesto que se convierte en el compuesto (I) por hidrólisis, etc. debido a un ácido gástrico, y similares. Un profármaco del compuesto (I) puede ser un compuesto obtenido al someter un grupo amino en el compuesto (I) a una acilación, alquilación o fosforilación (por ejemplo, un compuesto obtenido al someter un grupo amino en el compuesto (I) a una eicosanoilación, alanilación, pentilaminocarbonilación, (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilación, tetrahidrofuranilación, tetrahidropiranilación, pirrolidilmetilación, pivaloiloximetilación o ter-butilación); un compuesto obtenido al someter un grupo hidroxi en el

compuesto (I) a una acilación, alquilación, fosforilación o boración (por ejemplo, un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) a una acetilación, palmitoilación, propanoilación, pivaloilación, succinilación, fumarilación, alanilación, dimetilaminometilcarbonilación, o tetrahidropiranilación); un compuesto obtenido al someter un grupo carboxilo en el compuesto (I) a una esterificación o amidación (por ejemplo, un compuesto obtenido al someter un grupo carboxilo en el compuesto (I) a una etilesterificación, fenilesterificación, carboximetilesterificación, dimetilaminometilesterificación, pivaloiloximetilesterificación, etoxicarboniloxietilesterificación, ftalidilesterificación, (5-metil-2-oxo-1,3-dioxolen-4-il)metilesterificación, ciclohexiloxicarboniletilesterificación o metilamidación) y similares. Cualquiera de estos compuestos se puede producir a partir del compuesto (I) por medio de un método conocido *per se*.

Un profármaco del compuesto (I) puede ser un compuesto que se convierte en el compuesto (I) en condiciones fisiológicas, tal como se describen en Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

El compuesto (I) puede tener forma de un cristal, y la forma cristalina del cristal puede ser única o múltiple. El

cristal se puede producir mediante un método de cristalización conocido *per se*. En la presente especificación, el punto de fusión significa aquel que se midió con, por ejemplo, un aparato de punto de microfusión (Yanaco, MP-500D o Buchi, B-545) o un dispositivo DSC (calorimetría diferencial de barrido) (SEIKO, EXSTAR6000), y similares.

En general, los puntos de fusión varían según los aparatos de medición, las condiciones de medición, y similares. El cristal en la presente especificación puede mostrar diferentes valores del punto de fusión descrito en la presente especificación, siempre que estén dentro de un rango de error general.

El cristal del compuesto (I) es superior en propiedades fisicoquímicas (punto de fusión, solubilidad, estabilidad, etc.) y propiedades biológicas (farmacocinéticas (absorción, distribución, metabolismo, excreción), expresión de la eficacia, etc.) y, así, es extremadamente útil como medicamento.

El compuesto (I) puede ser un solvato (por ejemplo, hidrato) o un no solvato, los cuales están incluidos en el compuesto (I).

Un compuesto rotulado con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S, ^{125}I) y similares también están incluidos en el compuesto (I).

El compuesto (I) o uno de sus profármacos (de aquí

en adelante, a veces abreviado como el compuesto de la presente invención) muestra una baja toxicidad (por ejemplo, toxicidad aguda, toxicidad crónica, toxicidad genética, toxicidad reproductiva, cardiotoxicidad, interacción farmacológica, carcinogenicidad), y se puede usar como está o como composición farmacéutica en mezcla con un portador farmacéuticamente aceptable comúnmente conocido, etc., como un agente para la prevención o el tratamiento de las distintas enfermedades mencionadas más abajo, un sensibilizador de insulina y similares, en mamíferos (por ejemplo, humanos, ratones, ratas, conejos, perros, gatos, bovinos, caballos, cerdos, monos).

Aquí, como portador farmacológicamente aceptable se pueden usar varias sustancias portadoras orgánicas o inorgánicas utilizadas como material de preparación. Se incorporan como excipiente, lubricante, aglutinante y disgregante para preparaciones sólidas; solventes, auxiliares de disolución, agente de suspensión, agente de isotonicidad, tampón y agente suavizante para preparaciones líquidas y similares. De ser necesario, se pueden usar aditivos de preparación tales como conservantes, antioxidantes, colorantes, endulzantes, similares.

Como ejemplos preferidos de excipientes se pueden mencionar lactosa, sacarosa, D-manitol, D-sorbitol, almidón, α-almidón, dextrina, celulosa cristalina,

hidroxipropilcelulosa de baja sustitución, carboximetilcelulosa sódica, goma arábiga, pululano, ácido silícico anhidro ligero, silicato de aluminio sintético, metasilicato de aluminio y magnesio, y similares.

Como ejemplos preferidos del lubricante se pueden mencionar estearato de magnesio, estearato de calcio, talco, sílice coloidal, y similares.

Como ejemplos preferidos del aglutinante se pueden mencionar α-almidón, sacarosa, gelatina, goma arábiga, metilcelulosa, carboximetilcelulosa, carboximetilcelulosa sódica, celulosa cristalina, sacarosa, D-manitol, trehalosa, dextrina, pululano, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona y similares.

Como ejemplos preferidos del disgregante se pueden mencionar lactosa, sacarosa, almidón, carboximetilcelulosa, carboximetilcelulosa cálcica, croscarmelosa sódica, carboximetilalmidón sódico, ácido silícico anhidro liviano, hidroxipropilcelulosa de baja sustitución y similares.

Como ejemplos preferidos del solvente se pueden mencionar agua para inyección, suero fisiológico, solución de Ringer, alcohol, propilenglicol, polietilenglicol, aceite de sésamo, aceite de maíz, aceite de oliva, aceite de semillas de algodón, y similares.

Como ejemplos preferidos de los auxiliares de disolución se pueden mencionar polietilenglicol,

propilenglicol, D-manitol, trehalosa, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio, salicilato de sodio, etilacetato de sodio, y similares.

Como ejemplos preferidos del agente de suspensión se pueden mencionar tensioactivos tales como estеariltrietanolamina, laurilsulfato sódico, ácido laurilaminopropiónico, lecitina, cloruro de benzalconio, cloruro de bencetonio, monoestearato de glicerol, y similares; polímeros hidrofílicos tales como alcohol polivinílico, polivinilpirrolidona, carboximetilcelulosa sódica, metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa y similares; polisorbatos, aceite de ricino hidrogenado con polioxietileno, y similares.

Como ejemplos preferidos del agente de isotonicidad se pueden mencionar cloruro de sodio, glicerina, D-manitol, D-sorbitol, glucosa y similares.

Como ejemplos preferidos de tampón se pueden mencionar tampón tales como fosfato, acetato, carbonato, citrato y similares, y similares.

Como ejemplos preferidos de agente suavizante se pueden mencionar alcohol bencílico y similares.

Como ejemplos preferidos de conservante se pueden mencionar, p-oxibenzoatos, clorobutanol, alcohol bencílico, alcohol fenetílico, ácido deshidroacético, ácido sórbico y

similares.

Como ejemplos preferidos de antioxidante se puede mencionar sulfito, ascorbato y similares.

Como ejemplos preferidos de agente colorante se pueden mencionar colorantes de alquitrán alimenticios hidrosolubles (por ejemplo, colorantes alimenticios tales como Rojo alimenticio No. 2 y 3, Amarillo alimenticio No. 4 y 5, Azul alimenticio No. 1 y 2 y similares), tinturas de laca insolubles en agua (por ejemplo, sales de aluminio de los antes mencionados colores de alquitrán alimenticios hidrosolubles), tinturas naturales (por ejemplo, β-caroteno, clorofila, óxido de hierro rojo) y similares.

Como ejemplos preferidos de agente edulcorante, se pueden mencionar sacarina sódica, glicirricinato dipotásico, aspartame, estevia y similares.

Como forma de dosificación de la antes mencionada composición farmacéutica, por ejemplo, se pueden mencionar preparaciones orales tales como comprimidos (incluso comprimidos sublinguales, comprimidos orales de desintegración), cápsulas (incluso cápsulas blandas, microcápsulas), gránulos, polvo, sobres, jarabe, emulsión, suspensión y similares; y preparaciones parenterales tales como inyecciones (por ejemplo, inyección subcutánea, inyección intravenosa, inyección intramuscular, inyección intraperitoneal, infusión por goteo), preparaciones externas

(por ejemplo, preparaciones dérmicas, ungüentos), supositorios (por ejemplo, supositorios rectales, supositorios vaginales), pellets, preparaciones transnasales, preparaciones pulmonares (inhalantes), gotas oculares y similares. Se pueden administrar con seguridad por vía oral o parenteral.

Estas preparaciones pueden ser preparaciones de liberación controlada (por ejemplo, microcápsulas de liberación sostenida) tales como preparaciones de liberación inmediata, preparaciones de liberación sostenida, y similares.

La composición farmacéutica se puede producir por un método de uso convencional en el campo técnico de preparación, tal como un método descrito en Japanese Pharmacopoeia y similares.

Si bien el contenido del compuesto de la presente invención en la composición farmacéutica varía según la forma de dosificación, la dosis del compuesto de la presente invención y similares, es decir, por ejemplo, aproximadamente 0.1 a 100% en peso.

El compuesto de la presente invención se puede usar como sensibilizador de insulina, un agente para aumentar la sensibilidad de insulina, un regulador de función de receptor relacionado con retinoide, un ligando de receptor activado por proliferador de peroxisoma, un ligando de receptor de retinoide X y similares. Este regulador de función significa agonistas y antagonistas.

El compuesto de la presente invención tiene acción hipoglicémico, acción hipolipidémica, acción reductora de la insulina sanguínea, acción mejoradora de la resistencia a insulina, acción mejoradora de la sensibilidad a insulina y actividad reguladora de función de receptor relacionada con retinoide. La función reguladora puede ser un agonista parcial o antagonista parcial.

Aquí, los receptores relacionados con retinoide son factores de transcripción fijadores de ADN incluidos en los receptores nucleares y usan una molécula señal tal como vitamina liposoluble y similares como ligando, que pueden ser receptores monoméricos, receptores homodiméricos o receptores heterodiméricos.

Aquí, como receptores monoméricos, por ejemplo, se pueden mencionar receptor de retinoide O (en adelante abreviado ROR) α (No. de acceso GenBank L14611), RORβ (No. de acceso GenBank L14160), RORγ (No. de acceso GenBank U16997); Rev-erb α (No. de acceso GenBank M24898), Rev-erb β (No. de acceso GenBank L31785); ERRα (No. de acceso GenBank X51416), ERRβ (No. de acceso GenBank X51417); Ftz-FIα (No. de acceso GenBank S65876), Ftz-FI β (No. de acceso GenBank M81385); TIx (No. de acceso GenBank S77482); GCNF (No. de acceso GenBank U14666) y similares.

Como receptores homodiméricos, por ejemplo, se pueden mencionar homodímeros formados por receptores de

retinoide X (en adelante, a veces abreviado como RXR) α (No. de acceso GenBank X52773), RXRβ (No. de acceso GenBank M84820), RXRγ (No. de acceso GenBank U38480); COUPα (No. de acceso GenBank X12795), COUPβ (No. de acceso GenBank M64497), COUPγ (No. de acceso GenBank X12794); TR2α (No. de acceso GenBank M29960), TR2β (No. de acceso GenBank L27586); o HNF4α (No. de acceso GenBank X76930), HNF4γ (No. de acceso GenBank Z49826) y similares.

Como receptores heterodiméricos, por ejemplo, se pueden mencionar heterodímeros formados por los antes mencionados receptores de retinoide X (RXRα, RXRβ o RXRγ) y un tipo de receptor seleccionado de receptor de retinoide A (en adelante a veces abreviado como RAR) α (No. de acceso GenBank X06614), RARβ (No. de acceso GenBank Y00291), RARγ (No. de acceso GenBank M24857); receptor de hormona de glándula tiroides (en adelante a veces abreviado como TR) α (No. de acceso GenBank M24748), TRβ (No. de acceso GenBank M26747); receptor de vitamina D (VDR) (No. de acceso GenBank JO3258); receptor activado por proliferador de peroxisoma (en adelante a veces abreviado como PPAR) α (No. de acceso GenBank L02932), PPARβ (PPARδ)(No. de acceso GenBank U10375), PPARγ(No. de acceso GenBank L40904);LXRα (No. de acceso GenBank U22662), LXRβ (No. de acceso GenBank U14534); FXR (No. de acceso GenBank U18374); MB67 (No. de acceso GenBank L29263); ONR (No. de acceso GenBank X75163); y NURα (No. de acceso GenBank L13740),

NURβ (No. de acceso GenBank X75918) y NURγ (No. de acceso GenBank U12767).

El compuesto de la presente invención tiene una actividad de ligando superior (acción activadora) por receptores de retinoide X (RXRα, RXRβ, RXRγ) y receptores activados por proliferadores de peroxisomas (PPARα, PPARβ(PPARδ), PPARγ), de entre los antes mencionados receptores relacionados con retinoide, y es útil como agonista, un agonista parcial, un antagonista o un antagonista parcial de estos receptores.

Además, el compuesto de la presente invención tiene una actividad de ligando superior (acción activadora) para el receptor activado por proliferador de peroxisomas de los receptores heterodiméricos formados por receptor de retinoide X y receptor activado por proliferador de peroxisoma (por ejemplo, receptor heterodimérico formado por RXRα y PPARδ, receptor heterodimérico formado por RXRα y PPARγ).

En consecuencia, el compuesto de la presente invención de preferencia se usa como ligando de receptor activado por proliferador de peroxisoma o ligando de receptor de retinoide X.

El compuesto de la presente invención es útil como agente hipoglicémico libre de efectos secundarios tales como aumento de peso corporal, acumulación de adipocitos, hipertrofia cardíaca y similares.

El compuesto de la presente invención se puede usar, por ejemplo, como agente para la prevención o el tratamiento de diabetes (por ejemplo, diabetes tipo 1, diabetes tipo 1, diabetes gestacional, diabetes por obesidad); un agente para la prevención o tratamiento de hiperlipidemia (por ejemplo, hipertrigliceridemia, hipercolesterolemia, hipo-HDL-emia, hiperlipidemia posprandial); sensibilizador de insulina; un agente para aumentar la sensibilidad a insulina; un agente para la prevención o tratamiento de deterioro de tolerancia a glucosa [IGT (Deterioro de la Tolerancia a la Glucosa)]; y un agente para prevenir el progreso del deterioro de la tolerancia a la insulina a la diabetes.

Para los criterios diagnósticos de diabetes, Japan Diabetes Society informó nuevos criterios de diagnóstico.

De acuerdo con el presente informe, la diabetes es una condición que muestra cualquiera de un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 126 mg/dl, una prueba de tolerancia a 75 g de glucosa oral (75 g OGTT) a las 2 h (concentración de glucosa plasmática intravenosa) no inferior a 200 mg/dl, y un nivel de glucosa sanguínea no en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 200 mg/dl. Una condición que no cae bajo la antes mencionada diabetes y diferente de "una condición que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática

intravenosa) inferior a 110 mg/dl o una prueba de tolerancia a 75 g de glucosa oral (75 g OGTT) a las 2 h (concentración de glucosa plasmática intravenosa) inferior a 140 mg/dl" (tipo normal) se denomina "tipo margen".

Además, ADA (American Diabetes Association) y OMS informaron nuevos criterios diagnósticos de diabetes.

De acuerdo con estos informes, la diabetes es una condición que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 126 mg/dl y una prueba de tolerancia a 75 g de glucosa oral a las 2 h (concentración de glucosa plasmática intravenosa) no inferior a 200 mg/dl.

De acuerdo con los informes antes mencionados de ADA y OMS, el deterioro de tolerancia de glucosa es una condición que muestra un nivel de prueba de tolerancia a 75 g de glucosa oral a las 2 h (concentración de glucosa plasmática intravenosa) no inferior de 140 mg/dl e inferior a 200 mg/dl. De acuerdo con el informe de ADA, una condición que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 100 mg/dl e inferior a 126 mg/dl se denomina IFG (deterioro de glucosa en ayunas). Por otra parte, OMS define IFG (deterioro de glucosa en ayunas) como una condición que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 110 mg/dl e inferior a 126 mg/dl, y

la denomina IFG (deterioro de glucosa en ayunas).

El compuesto de la presente invención también se puede usar como agente para la prevención o tratamiento de diabetes, tipo margen, deterioro de tolerancia de glucosa, IFG (deterioro de glucosa en ayunas) y IFG (deterioro de glucosa en ayunas), tal como se determina de acuerdo con los nuevos antes mencionados criterios diagnósticos. Además, el compuesto de la presente invención puede prevenir el progreso del tipo margen, el deterioro de la tolerancia de glucosa, IFG (deterioro de glucosa en ayunas) o IFG (deterioro de glucemia en ayunas) a diabetes.

El compuesto de la presente invención también se puede usar como agente para la prevención o tratamiento, por ejemplo, de complicaciones diabéticas [por ejemplo, neuropatía, nefropatía, retinopatía, cataratas, macroangiopatía, osteopenia, coma diabético hiperosmolar, enfermedad infecciosa (por ejemplo, infección respiratoria, infección de las vías urinarias, infección gastrointestinal, infecciones de los tejidos blandos dérmicos, infección de los miembros inferiores), gangrena diabética, xerostomía, hipoacusia, trastornos cerebrovasculares, trastornos de la circulación sanguínea periférica], obesidad, osteoporosis, caquexia (por ejemplo, caquexia cancerosa, caquexia tuberculosa, caquexia diabética, caquexia de enfermedad sanguínea, caquexia de enfermedad endocrina, caquexia de enfermedad infecciosa o

caquexia debida a síndrome de inmunodeficiencia adquirida), hígado graso, hipertensión, síndrome de ovario poliquístico, enfermedad renal (por ejemplo, neuropatía diabética, nefritis glomerular, glomeruloesclerosis, síndrome nefrótico, nefroesclerosis hipertensiva, enfermedad renal de estadio terminal), distrofia muscular, infarto de miocardio, angina de pecho, accidente cerebrovascular (por ejemplo, infarto cerebral, apoplejía cerebral), síndrome de resistencia a insulina, Síndrome X, síndrome metabólico (patología con tres o más seleccionados de hipertrigliceridemia (TG), hipo-HDL-colesterolemia (HDL-C), hipertensión, sobrepeso abdominal y deterioro de la tolerancia a glucosa), hiperinsulinemia, trastorno sensitivo inducido por hiperinsulinemia, tumor (por ejemplo, leucemia, cáncer de mama, cáncer de próstata, cáncer de piel), síndrome de intestino irritable, diarrea aguda o crónica, enfermedades inflamatorias (por ejemplo, arterioesclerosis (por ejemplo, aterosclerosis), artritis reumatoide crónica, espondilitis deformante, osteoartritis, lumbago, gota, inflamación posquirúrgica o traumática, tumefacción, neuralgia, faringolaringitis, cistitis, hepatitis (inclusive esteatohepatitis no alcohólica), neumonía, pancreatitis, enfermedad inflamatoria intestinal, colitis ulcerativa, enfermedad pulmonar obstructiva crónica (EPOC)), síndrome de obesidad visceral, úlcera de pierna, asepsia, psoriasis y similares.

Además, el compuesto de la presente invención también se puede usar para aliviar condiciones tales como dolor abdominal, náuseas, vómitos, molestias del abdomen superior y similares, asociados con úlcera péptica, gastritis aguda o crónica, disquinesia biliar, colecistitis y similares, y similares.

El compuesto de la presente invención también se puede usar como agente para la prevención o tratamiento de una enfermedad inflamatoria que incluye TNF-α. Aquí, la enfermedad inflamatoria que incluye TNF-α es una enfermedad inflamatoria desarrollada por la presencia de TNF-α, que se puede tratar con un efecto inhibitorio de TNF-α. Como tal enfermedad inflamatoria, por ejemplo, se pueden mencionar complicaciones diabéticas (por ejemplo, retinopatía, nefropatía, neuropatía, macroangiopatía), artritis reumatoide crónica, espondilitis deformante, osteoartritis, lumbago, gota, inflamación posquirúrgica o traumática, tumefacción, neuralgia, faringolaringitis, cistitis, hepatitis, neumonía, lesión de membrana mucosa del estómago (incluso lesión de membrana mucosa estomacal causada por aspirina) y similares.

El compuesto de la presente invención tiene acción inhibitoria de apoptosis y también se puede usar como agente para la prevención o tratamiento de enfermedades que incluyen promoción de apoptosis. Como enfermedad que incluye la promoción de apoptosis, por ejemplo, se pueden mencionar

enfermedades virales (por ejemplo, sida, hepatitis fulminante), enfermedades neurodegenerativas (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, pigmentosa, degeneración cerebelar), mielodisplasia (por ejemplo, anemia aplásica), enfermedades isquémicas (por ejemplo, infarto de miocardio, apoplejía cerebral), enfermedades hepáticas (por ejemplo, hepatitis alcohólica, hepatitis B, hepatitis C), enfermedades articulares (por ejemplo, osteoartritis), aterosclerosis y similares.

El compuesto de la presente invención también se pueden usar para la reducción de grasa visceral, inhibición de la acumulación de grasa visceral, mejoramiento del metabolismo glúcido, mejoramiento del metabolismo lipídico, mejoramiento de la resistencia a insulina, inhibición de la producción de LDL oxidado, mejoramiento de metabolismo lipoproteíco, mejoramiento del metabolismo coronario, prevención o tratamiento de complicaciones cardiovasculares, prevención o tratamiento de complicaciones de insuficiencia cardiaca, reducción de flujo sanguíneo, prevención o tratamiento de anovulación, prevención o tratamiento de hirsutismo, prevención o tratamiento de hiperandrogenemia y similares.

El compuesto de la presente invención también se puede usar como prevención secundaria y supresión de la progresión de las diversas enfermedades antes mencionadas (por

ejemplo, eventos cardiovasculares tales como infarto de miocardio y similares).

Si bien la dosis del compuesto de la presente invención varía según el sujeto de la administración, la vía de administración, la enfermedad blanco, la condición y similares, por ejemplo, generalmente es de aproximadamente 0.005 a 50 mg/kg de peso corporal, de preferencia 0.01 a 2 mg/kg de peso corporal, con mayor preferencia 0.025 a 0.5 mg/kg de peso corporal, para la administración oral a pacientes diabéticos adultos, que de preferencia se administran de una a tres porciones por día.

El compuesto de la presente invención se puede usar en combinación con agentes farmacéuticos (en adelante abreviado como fármaco de combinación) tales como agentes terapéuticos para diabetes, agentes terapéuticos para complicaciones diabéticas, agentes terapéuticos para hiperlipidemia, agentes antihipertensivos, agentes antiobesidad, diuréticos, agentes quimioterapéuticos, agentes inmunoterapéuticos, agentes antitrombóticos, agentes terapéuticos para osteoporosis, agentes antidemencia, agentes para aliviar la disfunción eréctil, agentes terapéuticos para incontinencia urinaria o polaquiuria, agentes terapéuticos para disuria y similares. Estos fármacos de combinación pueden ser compuestos de bajo peso molecular, o proteínas, polipéptidos, anticuerpos, vacunas de alto peso molecular, y

similares.

El tiempo de administración del compuesto de la presente invención y el fármaco de combinación no están restringidos, y se pueden administrar a un sujeto de administración simultáneamente, o se pueden administrar en tiempos escalonados.

Como modo de administración del compuesto de la presente invención y el fármaco de combinación, se pueden mencionar los siguientes métodos: (1) El compuesto de la presente invención y el fármaco de combinación se formulan simultáneamente para dar una única preparación que se administra. (2) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos tipos de preparaciones que se administran simultáneamente por la misma vía de administración. (3) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos clases de preparaciones que se administran por la misma vía de administración a tiempos escalonados. (4) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos clases de preparaciones que se administran simultáneamente por las diferentes vías de administración. (5) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos clases de preparaciones que se administran por e diferentes vías de administración a tiempos

escalonados (por ejemplo, el compuesto de la presente invención y el fármaco de combinación se administran en este orden, o en orden inverso), y similares.

La dosis del fármaco de combinación se puede determinar adecuadamente en base a la dosis empleado clínicamente.

La proporción de mezclado del compuesto de la presente invención y un fármaco de combinación se pueden determinar adecuadamente según el sujeto de administración, la vía de administración, la enfermedad blanco, los síntomas, la combinación y similares. Si el sujeto de administración es humano, por ejemplo, se puede usar un fármaco de combinación en 0,01 a 100 partes en peso respecto de 1 parte en peso del compuesto de la presente invención.

Como agentes terapéuticos para diabetes se pueden mencionar preparaciones de insulina (por ejemplo, preparaciones de insulina animal extraídos de páncreas bovino y cerdo; preparaciones de insulina humana sintetizados genéticamente con *Escherichia coli*, levaduras; insulina cinc; insulina protamina cinc; fragmento o derivado de insulina (por ejemplo, INS-1), preparación oral de insulina), sensibilizador de insulina (por ejemplo, pioglitazona o su sal (de preferencia clorhidrato), rosiglitazona o una de sus sales (de preferencia maleato), netoglitazona, rivoglitazona (CS-011), FK-614, el compuesto descrito en WO01/38325, Tesaglitazar (AZ-

242), Ragaglitazar (NN-622), Muraglitazar (BMS-298585), Edaglitazone (BM-13-1258), Metaglidasen (MBX-102), Naveglitazar (LY-519818), MX-6054, LY-510929, AMG-131(T-131), THR-0921), inhibidores de α-glucosidasa (por ejemplo, voglibosa, acarbosa, miglitol, emiglitato, etc.), biguanidas (por ejemplo, fenformina, metformina, buformina o una de sus sales (por ejemplo, clorhidrato, fumarato, succinato)), secretagogos de insulina [sulfonilurea (por ejemplo, tolbutamida, glibenclamida, gliclazida, clorpropamida, tolazamida, acetohexamida, gliclopiramida, glimepirida, glipizida, glibuzol), repaglinida, nateglinida, mitiglinida o su sal de calcio hidratado], inhibidores de dipeptidilpeptidasa IV (por ejemplo, Vidagliptin (LAF237), P32/98, Sitagliptin (MK-431), P93/01, PT-100, Saxagliptin (BMS-477118), T-6666, TS-021), agonistas de β3 (por ejemplo, AJ-9677), agonistas de GPR40, agonistas de receptor GLP-1 [por ejemplo, GLP-1, agente GLP-1MR, NN-2211, AC-2993 (exendina-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH_2, CJC-1131], agonistas de amilina (por ejemplo, pramlintida), inhibidores de fosfotirosinfosfatasa (por ejemplo, vanadato sódico), inhibidores de gluconeogénesis (por ejemplo, inhibidores de glucogenofosforilasa, inhibidores de glucosa-6-fosfatasa, antagonistas de glucagon), inhibidores de SGLUT (cotransportador de glucosa sodio) (por ejemplo, T-1095), inhibidores de 11β-hidroxiesteroide deshidrogenasa (por ejemplo,

BVT-3498), adiponectina o sus agonistas, inhibidores de IKK (por ejemplo, AS-2868), fármacos mejoradores de resistencia de leptina, agonistas de receptor de somatostatina (compuestos descritos en WO01/25228, WO03/42204, WO98/44921, WO98/45285, WO99/22735 etc.), activadores de glucocinasa (por ejemplo, Ro-28-1675), GIP (péptido insulinotrópico dependiente de glucosa) y similares.

Los ejemplos de los agentes terapéuticos para complicaciones diabéticas incluyen inhibidores de aldosareductasa (por ejemplo, Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat, CT-112, ranirestat (AS-3201)), factores neurotróficos y sus fármacos incrementadores (por ejemplo, NGF, NT-3, BDNF, promotores de producción-secreción de neurotrofinas descritos en WO01/14372 (por ejemplo, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-[3-(2-metilfenoxi)propil]oxazol), inhibidores de PKC (por ejemplo, mesilato de ruboxistaurina)), inhibidores de AGE (por ejemplo, ALT946, pimagedina, bromuro de N-fenaciltiazolio (ALT-766), EXO-226, piridorina, piridoxamina), eliminadores de oxígeno activo (por ejemplo, ácido tióctico), vasodilatadores cerebrales (por ejemplo, tiapurida, mexiletina), agonista de receptor de somatostatina (por ejemplo, BIM23190), inhibidores de quinasa 1 (ASK-1) reguladora de señal de apoptosis y similares.

Los ejemplos de agentes terapéuticos para

hiperlipidemia incluyen inhibidores de HMG-CoA reductasa (por ejemplo, pravastatina, simvastatina, lovastatina, atorvastatina, fluvastatina, rosuvastatina, pitavastatina o una de sus sales (por ejemplo, sal de sodio, sal de calcio)), inhibidores de escualenosintetasa (por ejemplo, compuestos descritos en WO97/10224, tales como ácido N-[[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil]piperidin-4-acético), compuestos de fibrato (por ejemplo, bezafibrato, clofibrato, simfibrato, clinofibrato), inhibidores de ACAT (por ejemplo, avasimiba), eflucimiba)), resinas de intercambio aniónico (por ejemplo, colestiramina), probucol, fármacos de ácido nicotínico (por ejemplo, nicomol, niceritrol)), icosapentato de etilo, esteroles vegetales (por ejemplo, soisterol), γ-orizanol) y similares.

Los ejemplos de agentes antihipertensivos incluyen inhibidores de enzima convertidora de angiotensina (por ejemplo, captopril, enalapril, delapril), antagonistas de angiotensina II (por ejemplo, candesartan cilexetilo, losartan, eprosartan, valsartan, telmisartan, irbesartan, olmesartan medoxomilo, tasosartan, ácido 1-[[2'-(2,5-dihidro-5-oxo-4H-1,2,4-oxadiazol-3-il)bifenil-4-il]metil]-2-etoxi-1H-benzimidazol-7-carboxílico), bloqueadores de canales de calcio (por ejemplo, manidipina, nifedipina, nicardipina, amlodipina, efonidipina), abridores de canales de potasio (por ejemplo,

levcromacalima, L-27152, AL0671, NIP-121), clonidina y similares.

Los ejemplos de agentes antiobesidad incluyen agentes que actúan sobre el sistema nervioso central (por ejemplo, dexfenfluramina, fenfluramina, fentermina, sibutramina, amfepramona, dexamfetamina, mazindol, fenilpropanolamina, clobenzorex; antagonistas de receptor MCH (por ejemplo, SB-568849; SNAP-7941; compuestos descritos en WO01/82925 y WO01/87834); antagonistas de neuropéptido Y (por ejemplo, CP-422935); antagonistas de receptor de canabinoides (por ejemplo, SR-141716, SR-147778); antagonistas de ghrelina; inhibidores de 11β-hidroxiesteroide deshidrogenasa (por ejemplo, BVT-3498)), inhibidores de lipasa pancreática (por ejemplo, orlistat, cetilistat (ATL-962)), agonistas de β3 (por ejemplo, AJ-9677), anorexígenos peptídicos (por ejemplo, leptina, CNTF (factor neurotrópico ciliar)), agonistas de colecistoquinina (por ejemplo, lintitript, FPL-15849), inhibidores de alimentos (por ejemplo, P-57) y similares.

Los ejemplos de diuréticos incluyen derivados de xantina (por ejemplo, salicilato de sodio y teobromina, salicilato de calcio y teobromina), preparaciones de tiazida (por ejemplo, etiazida, ciclopentiazida, triclorometiazida, hidroclorotiazida, hidroflumetiazida, bencilhidroclorotiazida, penflutizida, politiazida, meticlotiazida), preparaciones antialdosterona (por ejemplo, espironolactona, triamtereno),

inhibidores de carbonato deshidratasa (por ejemplo, acetazolamida), preparaciones de clorobencensulfonamida (por ejemplo, clortalidona, mefrusida, indapamida), azosemida, isosorbida, ácido etacrínico, piretanida, bumetanida, furosemida y similares.

Los ejemplos de agentes quimioterapéuticos incluyen agentes alquilantes (por ejemplo, ciclofosfamida, ifosfamida), antagonistas metabólicos (por ejemplo, metotrexato, 5-fluorouracilo y uno de sus derivados), antibióticos antitumorales (por ejemplo, mitomicina, adriamicina), agentes antitumorales derivados de vegetales (por ejemplo, vincristina, vindesina, Taxol), cisplatino, carboplatino, etopósido y similares. De ellos, se prefieren Furtulon o NeoFurtulon, que son derivados 5-fluorouracilo y similares.

Los ejemplos de agentes inmunoterapéuticos incluyen componentes de microorganismos o bacterianos (por ejemplo, derivado de muramildipétido, picibanilo), polisacáridos con actividad potenciadora de inmunidad (por ejemplo, lentinano, esquizofilano, crestino), citocinas obtenidas mediante técnicas de ingeniería genética (por ejemplo, interferón, interleucina (IL)), factores estimulantes de colonias (por ejemplo, factor estimulante de colonias de granulocitos, eritropoyetina) y similares, de preferencia dados a interleucinas tales como IL-1, IL-2, IL-12 y similares.

Los ejemplos de agentes antitrombóticos incluyen

heparina (por ejemplo, heparina sódica, heparina cálcica, dalt-heparina sódica), warfarina (por ejemplo, warfarina potásica), fármacos antitrombina (por ejemplo, aragatrobano), agentes trombolíticos (por ejemplo, urocinasa, tisocinasa, alteplasa, nateplasa, monteplasa, pamiteplasa), inhibidores de agregación plaquetaria (por ejemplo, clorhidrato de ticlopidina, cilostazol, icosapentato de etilo, beraprost sódico, clorhidrato de sarpogrelato) y similares.

Los ejemplos de agentes terapéuticos para osteoporosis incluyen alfacalcidol, calcitriol, elcatonina, calcitonina de salmón, estriol, ipriflavona, risedronato disódico, pamidronato disódico, alendronato sódico hidratado, incadronato disódico y similares.

Los ejemplos de agentes antidemencia incluyen tacrina, donepezilo, rivastigmina, galantamina y similares.

Los ejemplos de agentes aliviadores de disfunción eréctil incluyen apomorfina, citrato de sildenafil y similares.

Los ejemplos de agentes terapéuticos para incontinencia urinaria o polaquiuria incluyen clorhidrato de flavoxato, clorhidrato de oxibutinina, clorhidrato de propiverina y similares.

Los ejemplos de agentes terapéuticos para disuria incluyen inhibidores de esterasa de acetilcolina (por ejemplo, distigmina) y similares.

Los ejemplos de fármacos de combinación incluyen

fármacos con acción aliviadora de caquexia establecida en modelos animales y situaciones clínicas, tales como inhibidores de ciclooxigenasa (por ejemplo, indometacina), derivados de progesterona (por ejemplo, acetato de megestrol), glucosteroides (por ejemplo, dexametasona), agentes de metoclopramida, agentes de tetrahidrocanabinol, agentes mejoradores del metabolismo graso (por ejemplo, ácido eicosapentanoico), hormonas de crecimiento, IGF-1, o anticuerpos contra factor inductor de caquexia tales como TNF-α, LIF, IL-6, oncostatina M y similares.

Como fármacos de combinación, se pueden mencionar fármacos promotores de regeneración nerviosa (por ejemplo, Y-128, VX853, prosaptida), antidepresivos (por ejemplo, desipramina, amitriptilina, imipramina), antiepilépticos (por ejemplo, lamotrigina), agentes antiarrítmicos (por ejemplo, mexiletina), ligandos de receptor de acetilcolina (por ejemplo, ABT-594), antagonistas de receptor de endotelina (por ejemplo, ABT-627), inhibidores de captación de monoaminas (por ejemplo, tramadol), analgésicos narcóticos (por ejemplo, morfina), agonistas de receptor de GABA (por ejemplo, gabapentina), agonistas de receptor de α2 (por ejemplo, clonidina), analgésicos locales (por ejemplo, capsaicina), fármacos ansiolíticos (por ejemplo, benzotiazepinas), agonistas de receptor de dopamina (por ejemplo, apomorfina), midazolam, quetoconazol y similares.

El fármaco de combinación de preferencia es una preparación de insulina, un sensibilizador de insulina, un inhibidor de α-glucosidasa, biguanida, secretagogo de insulina (de preferencia sulfonilurea) y similares.

Los antes mencionados fármacos de combinación se pueden usar en una mezcla de dos o más tipos en una proporción adecuada.

Si el compuesto de la presente invención se usa en combinación con un fármaco de combinación, se puede reducir la dosis de cada agente dentro de un rango de seguridad en consideración con sus efectos secundarios. En particular, las dosis de sensibilizador de insulinas, secretagogos de insulina y biguanidas se pueden reducir respecto de los niveles de dosis habituales. En consecuencia, es posible que se puedan prevenir con seguridad los efectos secundarios causados por estos agentes. Además, se pueden reducir las dosis de los agentes terapéuticos para complicaciones diabéticas, los agentes terapéuticos para hiperlipidemia y los agentes antihipertensivos, y como consecuencia, es posible prevenir efectivamente los efectos secundarios causados por estos agentes.

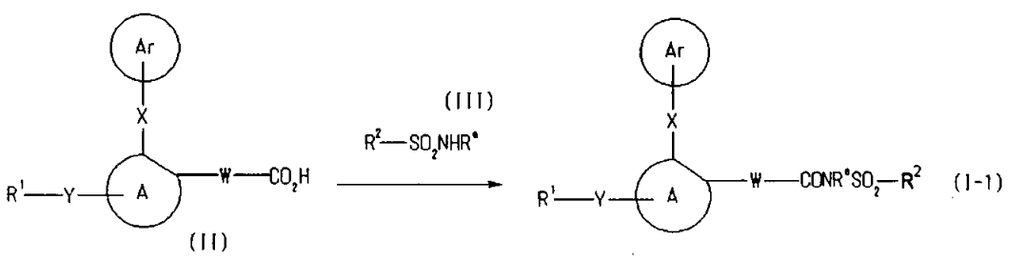
El método de producción del compuesto de la presente invención se explica a continuación.

El compuesto (I) se puede producir por un método conocido *per se*, por ejemplo el Método A al Método L, el

Método R que se muestran a continuación o uno de sus métodos análogos. En los siguientes métodos de producción respectivos, se puede usar el compuesto de material de partida como sal, y como tal sal, los ejemplos de las sales del compuesto representado por la fórmula (I).

El compuesto (I-1) de la fórmula (I) en donde Z es $-CONR^aSO_2-$ (R^a es como se definió antes) se puede producir, por ejemplo, por el siguiente Método A.

[Método A]



en donde los símbolos de la fórmula son como se definió antes.

En el presente método, el compuesto (I-1) se produce al someter al compuesto (II) a una reacción de amidación. La presente reacción se realiza por un método conocido *per se*, por ejemplo, un método que incluye directamente la condensación del compuesto (II) con el compuesto (III), o un método que incluye hacer reaccionar un derivado reactivo del compuesto (II) con el compuesto (III) y similares. Aquí, se pueden mencionar como derivado reactivo del compuesto (II), por ejemplo, anhídrido ácido, haluro ácido (por ejemplo, ácido

clorhídrico, ácido bromhídrico), imidazolida, anhídrido ácido mixto (por ejemplo, anhídrido con carbonato de metilo, carbonato de etilo, carbonato de isobutilo, ácido 2,4,6-triclorobenzoico o ácido 2-metil-6-nitrobenzoico) y similares.

El método incluye la condensación directa del compuesto (II) con el compuesto (III) que se realiza en la presencia de un agente de condensación, en un solvente que no influye adversamente sobre la reacción.

Como agente de condensación, por ejemplo, se pueden mencionar agentes de condensación generalmente conocidos tales como reactivos de condensación de carbodiimida (por ejemplo, diciclohexilcarbodiimida, diisopropilcarbodiimida, 1-etil-3-dimetilaminopropilcarbodiimida y sus clorhidratos); reactivos de condensación de ácido fosfórico tales como dietilcianofosfato, difenilfosforilazida y similares; N,N'-carbonildiimidazol, tetrafluoroborato de 2-cloro-1,3-dimetilimidazolio, clorodimetoxitriazina y similares.

Como solventes que no influyen adversamente sobre la reacción, por ejemplo, se pueden mencionar amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, agua y similares. Estos solventes se pueden usar como

una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (III) que se puede usar es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto del compuesto (II).

La cantidad del agente de condensación que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto del compuesto (II).

Cuando se usa un reactivo de condensación carbodiimida como agente de condensación, se utiliza un adecuado promotor de condensación (por ejemplo, 1-hidroxi-7-azabenzotriazol, 1-hidroxibenzotriazol, N-hidroxisuccinimida, N-hidroxiftalimida) según sea necesario para mejorar la eficiencia de la reacción. Cuando se usa un reactivo de condensación de ácido fosfórico como agente de condensación, generalmente se agrega una base de amina orgánica tal como trietilamina, diisopropiletilamina y similares para mejorar la eficiencia de la reacción.

La cantidad del promotor de condensación antes mencionado y la base de amina orgánica que se usa generalmente es de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto del compuesto (II).

La temperatura de reacción generalmente es de -30°C a 100°C.

El tiempo de reacción generalmente es de 0.5 a 60 h.

En un método que utiliza un derivado reactivo del

compuesto (II), cuando, por ejemplo, se usa un haluro ácido como derivado reactivo del compuesto (II), la reacción se lleva a cabo en la presencia de una base en un solvente que no influye adversamente sobre la reacción.

Como la base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 4-dimetilaminopiridina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares; y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares, acetato de etilo, agua y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (III) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (II).

La temperatura de reacción generalmente es de -30°C a 100°C.

El tiempo de reacción generalmente es de 0.5 a 20 h.

Cuando se usa anhídrido ácido mixto como derivado

reactivo del compuesto (II), se hace reaccionar el compuesto (II) con cualquiera de clorocarbonato (por ejemplo, clorocarbonato de metilo, clorocarbonato de etilo, clorocarbonato de isobutilo), cloruro ácido (por ejemplo, cloruro de 2,4,6-triclorobenzoilo) y anhídrido ácido (por ejemplo, anhídrido 2,4,6-triclorobenzoico, anhídrido 2-metil-6-nitrobenzoico) en presencia de una base (por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares), y luego se hace reaccionar con compuesto (III).

La cantidad de compuesto (III) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (II).

La temperatura de reacción generalmente es de -30°C a 100°C.

El tiempo de reacción generalmente es de 0.5 a 20 h.

Cuando se usa imidazolida como derivado reactivo de compuesto (II), el compuesto (II) se hace reaccionar con N,N'-carbonildiimidazol y también se hace reaccionar con compuesto (III) en la presencia de una base (por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5,4,0]undeca-7-eno y similares; las sales de metales alcalino tales como carbonato

de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares).

La cantidad de compuesto (III) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (II).

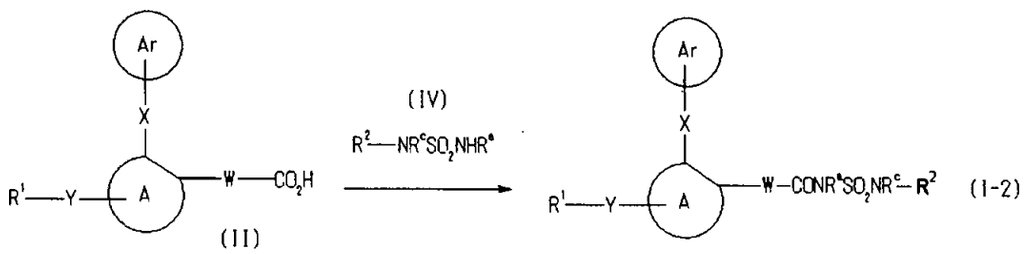
La temperatura de reacción generalmente es de -30°C a 100°C.

El tiempo de reacción generalmente es de 0.5 a 20 h.

El compuesto (III) que se usa como compuesto de material de partida en el antes mencionado Método A se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-2) de la fórmula (I) en donde Z es $-CONR^aSO_2NR^c-$ (R^a y R^c son como se definió antes) se puede producir, por ejemplo, por el siguiente Método B.

[Método B]



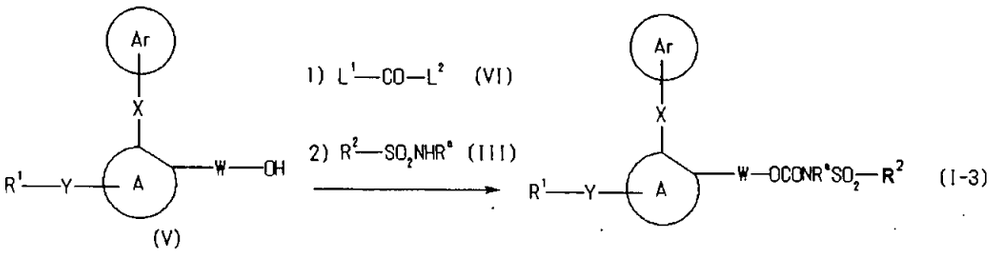
en donde los símbolos de la fórmula son como se definió antes.

En el presente método, el compuesto (II) se hace reaccionar con el compuesto (IV) para dar el compuesto (I-2). La presente reacción se realiza de la misma manera que en la reacción de amidación en el antes mencionado Método A.

El compuesto (IV) se pude producir de acuerdo con un método conocido *per se*.

El compuesto (I-3) de la fórmula (I) en donde Z es $-OCONR^aSO_2-$ (R^a es como se definió antes) se puede producir, por ejemplo, por el siguiente Método C o Método D.

[Método C]



en donde L^1 y L^2 son iguales o diferentes y cada uno es un grupo saliente, y otros símbolos son como se definió antes.

Aquí, como grupo saliente para L^1 o L^2, por ejemplo, se puede mencionar un grupo hidroxi, un átomo de halógeno, un grupo imidazolilo, un grupo succinimidooxi u $-OSO_2R^3$ (R^3 es un grupo alquilo con 1 a 4 átomos de carbono, un grupo arilo con 6 a 10 átomos de carbono opcionalmente sustituidos con un grupo alquilo con 1 a 4 átomos de carbono) y similares.

Como grupo alquilo con 1 a 4 átomos de carbono del "grupo alquilo con 1 a 4 átomos de carbono" y el "grupo arilo con 6 a 10 átomos de carbono opcionalmente sustituidos con un grupo alquilo con 1 a 4 átomos de carbono" para R^3, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo y ter-butilo tal como se mencionó, de preferencia de

metilo.

Como grupo arilo con 6 a 10 átomos de carbono se pueden mencionar el "grupo arilo con 6 a 10 átomos de carbono opcionalmente sustituido con un grupo alquilo con 1 a 4 átomos de carbono" para R^3, por ejemplo, fenilo y naftilo, de preferencia de fenilo.

R^3 es de particular preferencia metilo, tolilo y similares.

En el presente método, el compuesto (I-3) se produce a partir del compuesto (V). La presente reacción se realiza por un método conocido per se, por ejemplo, al hacer reaccionar el compuesto (V) con el compuesto (VI) en un solvente que no influye adversamente la reacción a temperatura ambiente durante aproximadamente 0.5 a 5 h, y se hace reaccionar el compuesto obtenido con el compuesto (III) en un solvente que no influye adversamente sobre la reacción a temperatura ambiente durante aproximadamente 0.5 a 24 h. En caso de necesidad, esta reacción se puede realizar en presencia de aproximadamente 1 a 5 equivalentes de una base.

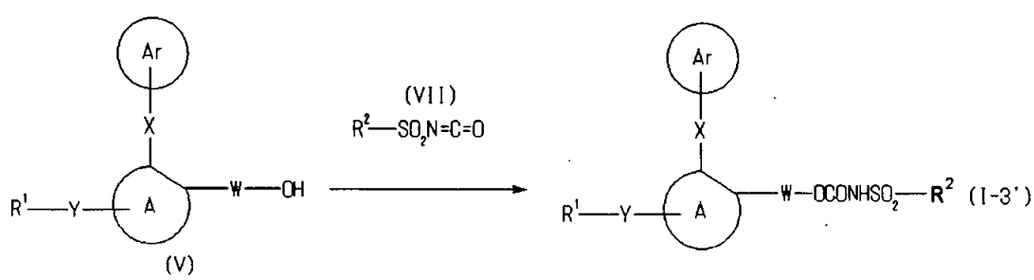
Como la base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, piridina, 4-dimetilaminopiridina y similares; sales de metales alcalino tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares; y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetato de etilo, agua y similares. Estos solventes se pueden usar como sus mezclas en una proporción adecuada.

La cantidad de compuesto (VI) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

La cantidad de compuesto (III) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

[Método D]



en donde los símbolos de la formula son como se definió antes.

En el presente método, el compuesto (V) se hace reaccionar con el compuesto (VII) para obtener, entre

compuestos (I-3), el compuesto (I-3') en donde R^a es un átomo de hidrógeno. La presente reacción se realiza por un método conocido *per se*, por ejemplo, al hacer reaccionar el compuesto (V) con el compuesto (VII) en un solvente que no influye adversamente sobre la reacción. De ser necesario, la presente reacción se puede realizar en presencia de aproximadamente 1 a 5 equivalentes de una base.

Como la base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 4-dimetilaminopiridina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares; y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, piridina, acetato de etilo, agua y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (VII) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

La temperatura de reacción generalmente es de -30°C a

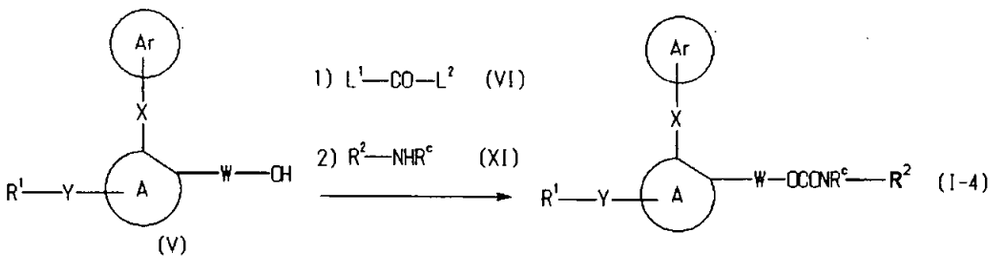
100°C.

El tiempo de reacción generalmente es de 0,5 a 20 h.

El compuesto (VII) que se usa como compuesto de material de partida en el antes mencionado Método D se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-4) de la fórmula (I) en donde Z es -$OCONR^c$- (R^c es como se definió con anterioridad) puede ser producido, por ejemplo, según el siguiente Método E.

[Método E]



en donde los símbolos en la fórmula son como se definió con anterioridad.

En el presente método, compuesto (I-4) se produce a partir del compuesto (V). La presente reacción se realiza mediante un método conocido *per se*, por ejemplo, al hacer reaccionar el compuesto (V) con compuesto (VI) en un solvente que no influye adversamente sobre la reacción a temperatura ambiente durante aproximadamente 0.5 a 5 h, y hacer reaccionar el compuesto obtenido con compuesto (XI) en un solvente que no influye adversamente sobre la reacción a temperatura ambiente durante aproximadamente 0.5 a 24 h. De ser necesario, la presente reacción se puede realizar en presencia de

aproximadamente 1 a 5 equivalentes de una base.

Como base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, piridina, 4-dimetilaminopiridina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares; y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetato de etilo, agua y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (VI) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

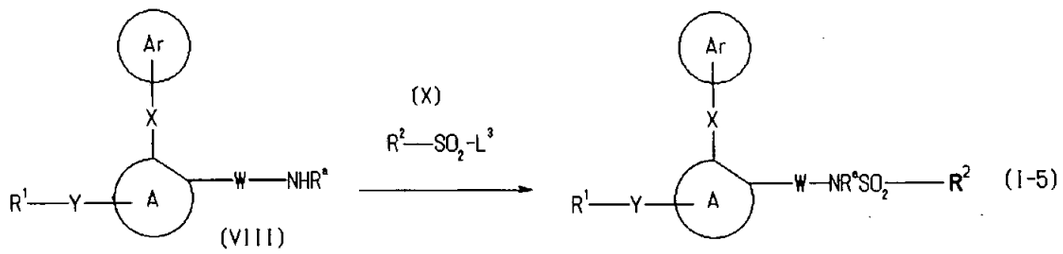
La cantidad de compuesto (XI) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

El compuesto (XI) que se usa como compuesto de material de partida en el antes mencionado Método E se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-5) de la fórmula (I) en donde Z es

$-NR^aSO_2-$ (R^a es como se definió con anterioridad) puede ser producido, por ejemplo, según el siguiente Método F o G.

[Método F]



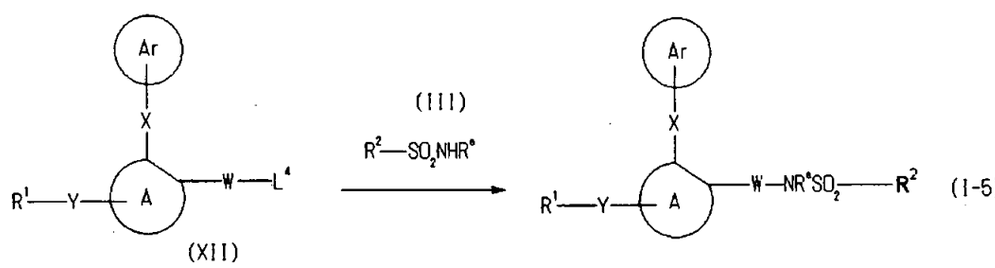
en donde L^3 es un grupo saliente, y otros símbolos son como se definió con anterioridad.

Como "grupo saliente" para L^3, se pueden mencionar los ejemplos antes mencionados L^1 y L^2. De ellos, se prefiere un átomo de halógeno y se prefiere particularmente un átomo de cloro.

En el presente método, el compuesto (VIII) se hace reaccionar con compuesto (X) para dar compuesto (I-5). La presente reacción se realiza de la misma manera que en la reacción de amidación en el antes mencionado Método A.

El compuesto (X) que se usa como compuesto de material de partida en el antes mencionado Método F se puede producir de acuerdo con un método conocido *per se*.

[Método G]



en donde L^4 es un grupo saliente, y otros símbolos

son como se definió con anterioridad.

Como "grupo saliente" para L^4, se pueden mencionar los ejemplos antes mencionados L^1 y L^2. De ellos se prefieren un átomo de halógeno y $-OSO_2R^3$ y un átomo de cloro y un grupo metansulfoniloxi son de particular preferencia.

En el presente método, el compuesto (XII) se hace reaccionar con el compuesto (III) para dar el compuesto (I-5).

Cuando L^4 es un grupo hidroxi, la presente reacción se realiza por un método conocido *per se*, por ejemplo, el método descrito en Synthesis, página 1 (1981), o un método análogo. En otras palabras, la presente reacción generalmente se lleva a cabo en presencia de un compuesto de fósforo orgánico y un agente electrofílico en un solvente que no influye adversamente sobre la reacción.

Como compuesto de fósforo orgánico se puede mencionar, por ejemplo, trifenilfosfina, tributilfosfina y similares.

Como agente electrofílico se pueden mencionar, por ejemplo, azodicarboxilato de dietilo, azodicarboxilato de diisopropilo, 1,1'-azodicarbonildipiperidina y similares.

Las cantidades de compuesto de fósforo orgánico y el agente electrofílico que se puede usar son de preferencia aproximadamente 1 a aproximadamente 5 equivalentes molares respecto de compuesto (XII).

La cantidad de compuesto (III) que se usa es de

preferencia aproximadamente 1 a aproximadamente 5 equivalentes molares respecto de compuesto (XII).

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; amidas tales como N,N-dimetilformamida y similares; sulfóxidos tales como dimetilsulfóxido y similares; y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La temperatura de reacción generalmente es de aproximadamente -50°C a aproximadamente 150°C, de preferencia aproximadamente -10°C a aproximadamente 100°C.

El tiempo de reacción generalmente es de aproximadamente 0,5 a aproximadamente 20 h.

Cuando L^4 es un átomo de halógeno u $-OSO_2R^3$, la presente reacción se realiza de acuerdo con un método convencional en presencia de una base en un solvente que no influye adversamente sobre la reacción.

Como la base, por ejemplo, se pueden mencionar sales de metales alcalinos tales como hidróxido de potasio, hidróxido de sodio, carbonato de hidrógeno y sodio, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina,

1,8-diazabiciclo[5,4,0]undec-7-eno y similares; hidruros de metales tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos de C_{1-6} de metales alcalinos tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

La cantidad de la base que se usa es de preferencia aproximadamente 1 a aproximadamente 5 equivalentes molares, respecto del compuesto (XII).

La cantidad de compuesto (III) que se usa es de preferencia aproximadamente 1 a aproximadamente 5 equivalentes molares, respecto del compuesto (XII).

Como el solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; cetonas tales como acetona, 2-butanona y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida y similares; sulfóxidos tales como dimetilsulfóxido y similares y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La temperatura de reacción generalmente es de aproximadamente -50°C a aproximadamente 150°C, de preferencia aproximadamente -10°C a aproximadamente

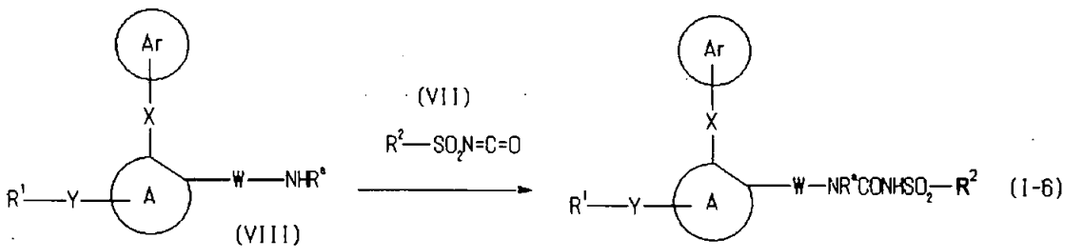
100°C.

El tiempo de reacción generalmente es de aproximadamente 0.5 a aproximadamente 20 h.

El compuesto (XII) usado como compuesto material de partida en el antes mencionado Método G se puede producir por un método conocido *per se* a partir del antes mencionada compuesto (V).

El compuesto (I-6) de la fórmula (I) en donde Z es $-NR^aCONR^bSO_2-$ (R^a y R^b son como se definió antes), y R^b es un átomo de hidrógeno puede ser producido, por ejemplo, según el siguiente Método H.

[Método H]

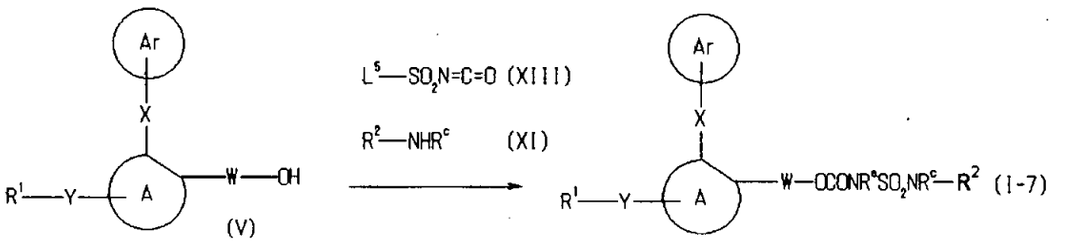


en donde los símbolos en la fórmula son como se definió con anterioridad.

En el presente método, el compuesto (VIII) se hace reaccionar con compuesto (VII) para dar el compuesto (I-6). La presente reacción se realiza de la misma manera que en el antes mencionado Método D.

El compuesto (I-7) de la fórmula (I) en donde Z es $-OCONR^aSO_2NR^c-$ (R^a y R^c como se definió antes) puede ser producido, por ejemplo, según el siguiente Método I.

[Método I]



en donde L^5 es un grupo saliente, y otros símbolos son como se definió con anterioridad.

Como "grupo saliente" para L^5, se pueden mencionar los ejemplos antes mencionados L^1 y L^2. De ellos, se prefiere un átomo de halógeno y un átomo de cloro es de particular preferencia.

En el presente método, el compuesto (I-7) se produce a partir del compuesto (V). La presente reacción se realiza mediante un método conocido *per se*, por ejemplo, al hacer reaccionar el compuesto (V) con compuesto (XIII) en un solvente que no influye adversamente sobre la reacción a temperatura ambiente durante aproximadamente 0.5 a 5 h, y hacer reaccionar el compuesto obtenido con compuesto (XI) en un solvente que no influye adversamente sobre la reacción a temperatura ambiente durante aproximadamente 0.5 a 24 h. De ser necesario, la presente reacción se puede realizar en presencia de aproximadamente 1 a 5 equivalentes de una base.

Como base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, piridina, 4-

dimetilaminopiridina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares, y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares, acetonitrilo, piridina, acetato de etilo, agua y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (XIII) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

La cantidad de compuesto (XI) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

La temperatura de reacción generalmente es de -30°C a 100°C.

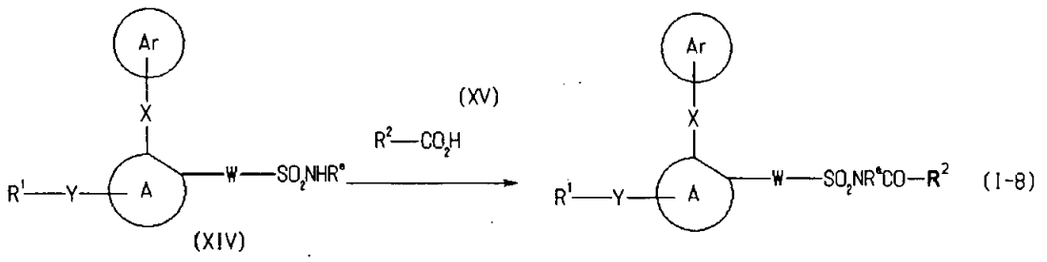
El tiempo de reacción generalmente es de 0.5 a 20 h.

El compuesto (XIII) que se usa como compuesto de material de partida en el antes mencionado Método I se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-8) de la fórmula (I) en donde Z es $-SO_2NR^aCO-$ (R^a es como se definió con anterioridad) puede ser

producido, por ejemplo, según el siguiente Método J.

[Método J]



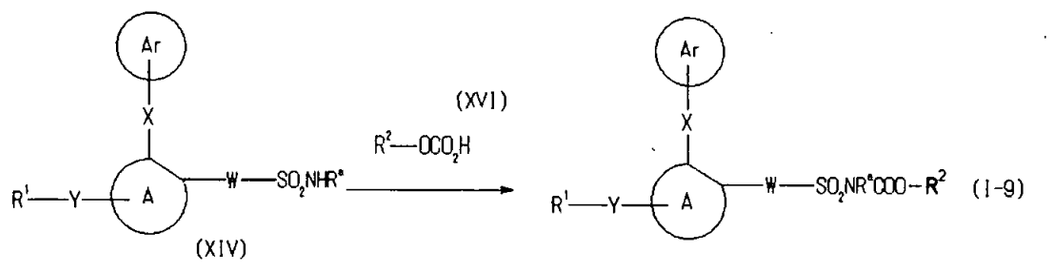
en donde los símbolos en la fórmula son como se definió con anterioridad.

En el presente método, el compuesto (I-8) se produce al hacer reaccionar el compuesto (XIV) con el compuesto (XV). La presente reacción se realiza de la misma manera que en la reacción de amidación descrita en el antes mencionado Método A.

El compuesto (XV) que se usa como compuesto de material de partida en el antes mencionado Método J se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-9) de la fórmula (I) en donde Z es $-SO_2NR^aCOO-$ (R^a es como se definió con anterioridad) puede ser producido, por ejemplo, según el siguiente Método K.

[Método K]



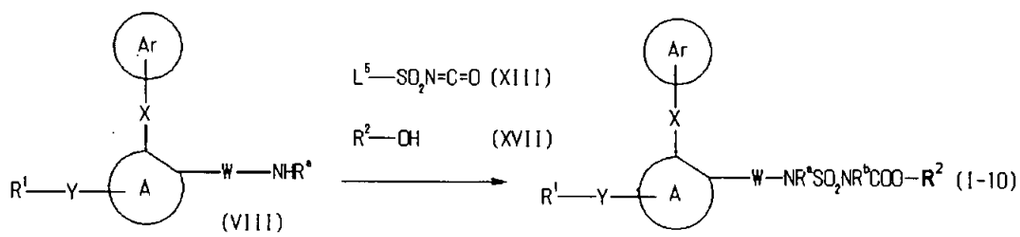
en donde los símbolos en la fórmula son como se definió con anterioridad.

En el presente método, se produce el compuesto (I-9) al hacer reaccionar el compuesto (XIV) con compuesto (XVI). La presente reacción se realiza de la misma manera que en la reacción de amidación descrita en el antes mencionado Método A.

El compuesto (XVI) que se usa como compuesto de material de partida en el antes mencionado Método K se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-10) de la fórmula (I) en donde Z es $-NR^aSO_2NR^bCOO-$ (R^a y R^b son como se definió antes) puede ser producido, por ejemplo, según el siguiente Método L.

[Método L]



en donde los símbolos en la fórmula son como se definió con anterioridad.

En el presente método, el compuesto (I-10) se produce a partir del compuesto (VIII). La presente reacción se realiza mediante un método conocido *per se*, por ejemplo, al hacer reaccionar el compuesto (VIII) con compuesto (XIII) en un solvente que no influye adversamente sobre la reacción a temperatura ambiente durante aproximadamente 0.5 a 5 h, y hacer reaccionar el compuesto obtenido con compuesto (XVII) en un solvente que no influye adversamente sobre la reacción a

temperatura ambiente durante aproximadamente 0.5 a 24 h. De ser necesario, la presente reacción se puede realizar en presencia de aproximadamente 1 a 5 equivalentes de una base.

Como base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, piridina, 4-dimetilaminopiridina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares, y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares, acetonitrilo, piridina, acetato de etilo, agua y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (XIII) que se pueden usar es de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (VIII).

La cantidad de compuesto (XVII) que se pueden usar es de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (VIII).

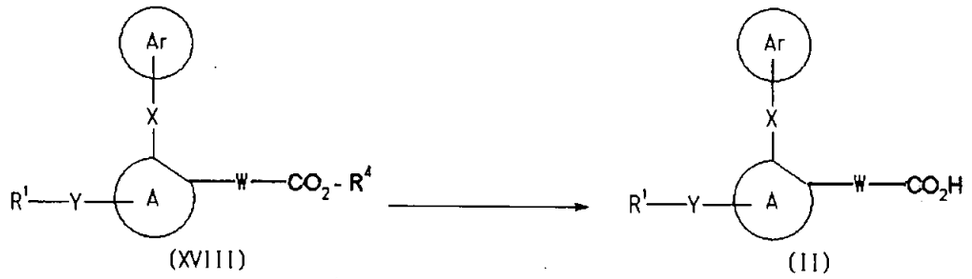
La temperatura de reacción generalmente es de -30°C a 100°C.

El tiempo de reacción generalmente es de 0.5 a 20 h.

El compuesto (XVII) que se usa como compuesto de material de partida en el antes mencionado Método L se puede producir de acuerdo con un método conocido *per se*.

Compuesto (II) que se usa como compuesto de material de partida en el antes mencionado Método A y Método B puede ser producido, por ejemplo, según el siguiente Método M.

[Método M]



en donde R^4 es un grupo hidrocarburo opcionalmente sustituido, y otros símbolos son como se definió antes.

Aquí, como "grupo hidrocarburo opcionalmente sustituido" para el antes mencionado R^4, se pueden mencionar los ejemplos antes mencionados R^1. R^4 es de preferencia un grupo alquilo de C_{1-6}, con mayor preferencia metilo, etilo y similares.

En el presente método, el compuesto (II) se produce al someter el compuesto (XVIII) a una reacción de hidrólisis. La presente reacción se realiza por un método convencional en la presencia de un ácido o una o base en un solvente que contiene agua.

Como ácido, por ejemplo, se pueden mencionar ácidos

inorgánicos tales como ácido clorhídrico, ácido sulfúrico, ácido bromhídrico y similares; ácidos orgánicos tales como ácido acético y similares; y similares.

Como la base, por ejemplo, se pueden mencionar carbonates de metales alcalinos tales como carbonato de potasio, carbonato de sodio y similares; alcóxidos de C_{1-6} de metales alcalinos tales como metóxido de sodio y similares; hidróxidos de metales alcalinos tales como hidróxido de potasio, hidróxido de sodio, hidróxido de litio y similares; y similares.

La cantidad de ácido o base que se usa es generalmente de una cantidad en exceso respecto del compuesto (XVIII). La cantidad del ácido que se usa es de preferencia aproximadamente 2 a aproximadamente 50 equivalentes respecto del compuesto (XVIII) y la cantidad de la base que se usa es de aproximadamente 1.2 a aproximadamente 5 equivalentes respecto del compuesto (XVIII).

Como solvente que contiene agua, por ejemplo, se pueden mencionar solventes mixtos de agua con uno o más tipos de solventes seleccionados de alcoholes tales como metanol, etanol y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; dimetilsulfóxido, acetona y similares; y similares.

La temperatura de reacción generalmente es de aproximadamente -20°C a aproximadamente 150°C, de preferencia

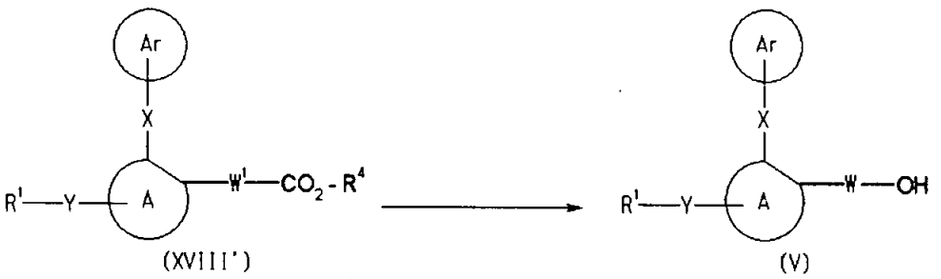
aproximadamente -10°C a aproximadamente 100°C.

El tiempo de reacción generalmente es de aproximadamente 0,1 a aproximadamente 20 h.

El compuesto (XVIII) que se usa como compuesto de material de partida en el antes mencionado Método M se puede producir, por ejemplo, por el Método P mencionado a continuación o uno de sus métodos análogos.

El compuesto (V) que se usa como compuesto de material de partida en el antes mencionado Método C, Método D, Método E y Método I puede ser producido, por ejemplo, según el siguiente Método N.

[Método N]



en donde W^1 es un grupo hidrocarburo divalente opcionalmente sustituido con 1 a 19 átomos de carbono, y otros símbolos son como se definió antes.

Como "grupo hidrocarburo divalente opcionalmente sustituido con 1 a 19 átomos de carbono" para W^1, se puede usar el antes mencionado "grupo hidrocarburo divalente opcionalmente sustituido con 1 a 20 átomos de carbono" de W, que contiene 1 a 19 átomos de carbono que constituye el grupo hidrocarburo.

En el presente método, el compuesto (V) se produce al sustituir el compuesto (XVIII') en una reacción de reducción. La presente reacción generalmente se realiza en presencia de un agente reductor en un solvente que no influye adversamente sobre la reacción.

Como agente reductor, por ejemplo, se pueden mencionar compuestos de hidrógeno y metal tales como hidruro de bis(2-metoxietoxi)aluminio y sodio, hidruro de diisobutilaluminio y similares; complejos de compuestos de hidrógeno y metal tales como borohidruro de sodio, cianoborohidruro de sodio, hidruro de aluminio y litio, hidruro de aluminio y sodio y similares; y similares.

La cantidad del agente reductor que se usa es generalmente de 1 a 20 equivalentes molares respecto de compuesto (XVIII').

Como solvente que no influye adversamente sobre la reacción, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, butanol, isobutanol, ter-butanol y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; hidrocarburos halogenados tales

como diclorometano, cloroformo, 1,2-dicloroetano, 1,1,2,2-tetracloroetano y similares; y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

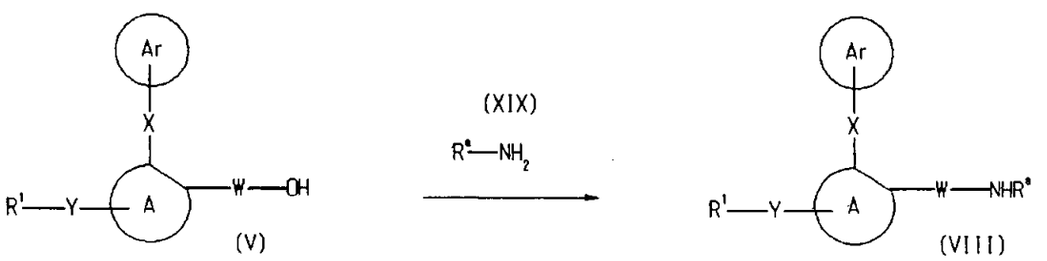
La temperatura de reacción generalmente es de -70°C a 150°C, de preferencia -20°C a 100°C.

El tiempo de reacción generalmente es de 0.1 a 100 h, de preferencia 0.1 a 40 h.

El compuesto (XVIII') que se usa como compuesto de material de partida en el antes mencionado Método N puede ser producido, por ejemplo, por el Método mencionado a continuación o uno de sus métodos análogos.

El compuesto (VIII) que se usa como compuesto de material de partida en el antes mencionado Método F, Método H y Método L puede ser producido, por ejemplo, según el siguiente Método O.

[Método O]



en donde los símbolos en la fórmula son como se definió con anterioridad.

En el presente método, el compuesto (VIII) se produce al someter el compuesto (V) a una reacción de alquilación. La presente reacción se realiza mediante un

método conocido *per se*, al hacer reaccionar un compuesto obtenido al convertir el grupo hidroxi del compuesto (V) a un grupo saliente (átomo de halógeno u $-OSO_2R^3$) con compuesto (XIX) en la presencia de una base en un solvente que no influye adversamente sobre la reacción.

Como base, por ejemplo, se pueden mencionar aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, piridina, 4-dimetilaminopiridina y similares; sales de metales alcalinos tales como carbonato de hidrógeno y sodio, carbonato de sodio, carbonato de potasio y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos de C_{1-6} de metales alcalinos tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares; y similares.

Como solvente que no influye adversamente sobre la reacción, se puede mencionar por ejemplo, hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares, acetonitrilo, piridina, acetato de etilo, agua y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de compuesto (XIX) que se usa es generalmente de 0.1 a 10 equivalentes molares, de preferencia 0.3 a 3 equivalentes molares, respecto de compuesto (V).

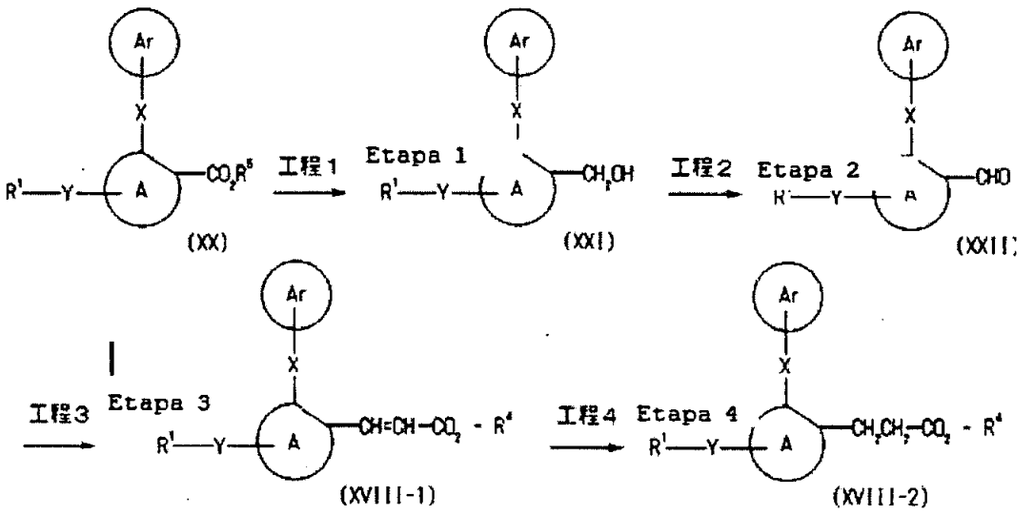
La temperatura de reacción generalmente es de -30°C a 100°C.

El tiempo de reacción generalmente es de 0,5 a 20 h.

Compuesto (XIX) que se usa como compuesto de material de partida en el antes mencionado Método O se puede producir de acuerdo con un método conocido *per se*.

De los compuestos (XVIII) que se usan como compuestos de material de partida en el antes mencionado Método M, el compuesto (XVIII-1) y (XVIII-2) en donde W es -CH=CH- o $-CH_2CH_2-$ puede ser producido, por ejemplo, según el siguiente Método P.

[Método P]



en donde R^5 es un grupo alquilo de C_{1-6}, y otros símbolos son como se definió antes.

[Etapa 1]

En esta etapa, el compuesto (XXI) se produce al

someter el compuesto (XX) a una reacción de reducción. La presente reacción se realiza de la misma manera que en el antes mencionado Método N.

El compuesto (XX) puede ser producido, por ejemplo, por el método descrito en WO 01/38325 y similares, o uno de sus métodos análogos.

[Etapa 2]

En esta etapa, el compuesto (XXII) es producido al someter al compuesto (XXI) a una reacción de oxidación. Esta reacción generalmente se realiza en presencia de un oxidante en un solvente que no influye adversamente sobre la reacción.

Como oxidante, se pueden mencionar, por ejemplo, oxidantes de metal tales como dióxido de manganeso, clorocromato de piridinio, diclorocromato de piridinio, óxido de rutenio y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad del oxidante de metal que se usa es generalmente de 1 a 50 equivalentes molares, de preferencia 1 a 10 equivalentes molares, respecto de compuesto (XXI).

La temperatura de reacción generalmente es de aproximadamente -50°C a aproximadamente 150°C, de preferencia aproximadamente -10°C a aproximadamente 100°C.

El tiempo de reacción generalmente es de aproximadamente 0.5 a aproximadamente 20 h.

El compuesto (XXII) también se puede producir al disolver el compuesto (XXI) en dimetilsulfóxido o un solvente mixto de dimetilsulfóxido e hidrocarburo halogenado (por ejemplo, cloroformo, diclorometano) en una proporción adecuada, con agregado de un complejo de trióxido de azufre y piridina o cloruro de oxalilo, y hacer reaccionar con una base orgánica (por ejemplo, trietilamina, N-metilmorfolina).

La cantidad de complejo de trióxido de azufre y piridina o cloruro de oxalilo que se usa es de 1 a 50 equivalentes molares, de preferencia 1 a 10 equivalentes molares, respecto de compuesto (XXI).

La cantidad de la base orgánica que se usa es de 1 a 50 equivalentes molares, de preferencia 1 a 10 equivalentes molares, respecto de compuesto (XXI).

La temperatura de reacción generalmente es de aproximadamente -100°C a aproximadamente 150°C, de preferencia aproximadamente -70°C a aproximadamente 100°C.

El tiempo de reacción generalmente es de aproximadamente 0.5 a aproximadamente 20 h.

[Etapa 3]

En esta etapa, el (XVIII-1) se produce al someter el compuesto (XXII) en una reacción de adición de carbono. La presente reacción generalmente se realiza con un reactivo de fósforo orgánico en un solvente que no influye adversamente sobre la reacción, y en presencia de una base.

Como la base, por ejemplo, se pueden mencionar sales de metales alcalinos tales como hidróxido de potasio, hidróxido de sodio, carbonato de hidrógeno y sodio, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5,4,0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos de C_{1-6} de metales alcalinos tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

Como reactivo de fósforo orgánico, por ejemplo, se puede mencionar fosfonoacetato de trimetilo, dietilfosfonoacetato de metilo, fosfonoacetato de trietilo, dietilfosfonoacetato de ter-butilo y similares.

Como solvente que no influye adversamente sobre la reacción, por ejemplo, se pueden mencionar hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter

diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como dimetilsulfóxido y similares; alcoholes tales como metanol, etanol, isopropanol, ter-butanol y similares; y similares. Estos solventes se pueden usar como una de sus mezclas en una proporción adecuada.

La cantidad de la base que se usa es generalmente de 1 a 50 equivalentes molares, de preferencia 1 a 10 equivalentes molares, respecto del compuesto (XXII).

La cantidad del reactivo de fósforo orgánico que se usa es generalmente de 1 a 50 equivalentes molares, de preferencia 1 a 10 equivalentes molares, respecto del compuesto (XXII).

La temperatura de reacción generalmente es de aproximadamente -100°C a aproximadamente 150°C, de preferencia aproximadamente -10°C a aproximadamente 100°C.

El tiempo de reacción generalmente es de aproximadamente 0,5 a aproximadamente 20 h.

[Etapa 4]

En esta etapa, el compuesto (XVIII-2) se produce al someter el compuesto (XVIII-1) a una reacción de hidrogenación.

La reacción se puede hacer reaccionar, por ejemplo,

en la presencia de un catalizador metálico tal como paladio-carbono, negro de paladio, cloruro de paladio, óxido de platino, negro de platino, platino-paladio, níquel de Raney, cobalto de Raney y similares y una fuente de hidrógeno, en un solvente que no influye adversamente sobre la reacción.

La cantidad de catalizador metálico que se usa es generalmente de 0.001 a 1000 equivalentes molares, de preferencia 0.01 a 100 equivalentes molares, respecto de compuesto (XVIII-1).

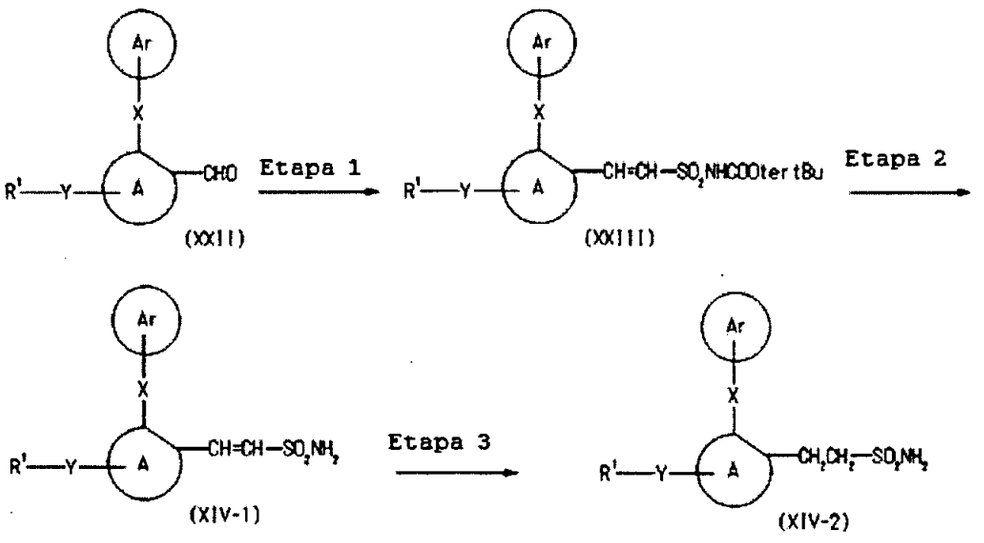
Como fuente de hidrógeno, por ejemplo, se puede mencionar gas hidrógeno, ácido fórmico, sal amina de ácido fórmico, fosfinato, hidracina y similares.

Como solvente que no influye adversamente sobre la reacción se pueden usar los ejemplificados en la antes mencionada etapa 1.

La temperatura de reacción y el tiempo de reacción son iguales a los de la antes mencionada etapa 1.

De los compuestos (XIV) que se usan como compuesto de material de partida en el antes mencionado Método J y Método K, el compuesto (XIV-1) y (XIV-2), en donde W es -CH=CH- o $-CH_2CH_2-$ y R^a es un átomo de hidrógeno puede ser producido, por ejemplo, según el siguiente Método Q.

[Método Q]



en donde los símbolos en la fórmula son como se definió con anterioridad.

[Etapa 1]

En esa etapa, el compuesto (XXIII) se produce a partir del compuesto (XXII). La presente reacción se realiza mediante un método conocido *per se*, por ejemplo, por el método descrito en Synthesis, página 2321 (2003), o un método análogo.

[Etapa 2]

En esta etapa, el compuesto (XIV-1) se produce al someter el compuesto (XXIII) a una reacción de protección. La presente reacción se realiza mediante un método conocido *per se*.

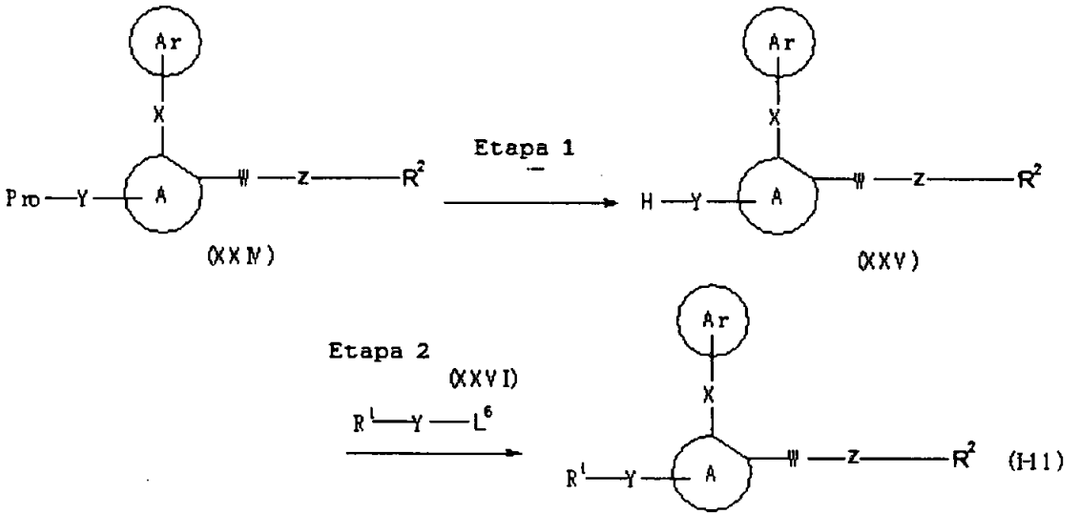
[Etapa 3]

En esta etapa, el compuesto (XIV-2) se produce al someter el compuesto (XIV-1) a una reacción de hidrogenación.

La presente reacción se realiza de la misma manera que en la reacción descrita en el antes mencionado Método P, etapa 4.

El compuesto (I-11) de la fórmula (I) en donde Y es un átomo de oxígeno o un átomo de azufre puede ser producido, por ejemplo, según el siguiente Método R.

[Método R]



en donde Pro es un grupo protector hidroxi o un grupo protector mercapto, L^6 es un grupo saliente, y otros símbolos son como se definió con anterioridad.

Aquí, como grupo protector hidroxi para Pro, por ejemplo, se puede mencionar un grupo alquilo de C_{1-6}, un grupo aralquilo de C_{7-20} (por ejemplo, bencilo, tritilo), un grupo formilo, un grupo alquilo C_{1-6} carbonilo, un grupo benzoilo, un grupo aralquilo de C_{7-10} carbonilo (por ejemplo, bencilcarbonilo), un grupo 2-tetrahidropiranilo, un grupo tetrahidrofuranilo o un grupo sililo sustituido (por ejemplo,

un grupo trialquil de C_{1-6} sililo tal como trimetilsililo, trietilsililo, ter-butildimetilsililo y ter-butildietilsililo; ter-butildifenilsililo) y similares, cada uno opcionalmente con sustituyentes. Tal como se usa en la presente, como sustituyente se pueden usar, por ejemplo, un átomo de halógeno, un grupo alquilo de C_{1-6}, un grupo fenilo, un grupo aralquilo de C_{7-10} (por ejemplo, bencilo), un grupo alcoxi de C_{1-6}, un grupo nitro y similares. La cantidad del sustituyente es 1 a 4.

Como grupo protector mercapto para Pro, por ejemplo, se puede mencionar un grupo alquilo de C_{1-6}, un grupo aralquilo de C_{7-20} (por ejemplo, bencilo, tritilo) y similares, cada uno opcionalmente con sustituyente(s). Tal como se usó en la presente, se puede usar como sustituyente, por ejemplo, un átomo de halógeno, un grupo alquilo de C_{1-6}, un grupo fenilo, un grupo aralquilo de C_{7-10} (por ejemplo, benciló), un grupo alcoxi de C_{1-6}, un grupo alquilo de C_{1-6} carbonilo, un grupo nitro y similares. La cantidad de sustituyentes es de 1 a 4.

Como "grupo saliente" para L6, se pueden mencionar los ejemplificados en los antes mencionados L1 y L2. De ellos se prefiere, un átomo de halógeno u -OSO2R3 (R3 es un grupo alquilo con 1 a 4 átomos de carbono o un grupo arilo con 6 a 10 átomos de carbono opcionalmente sustituido con un grupo alquilo con 1 a 4 átomos de carbono), y un átomo de cloro y metansulfoniloxi son de particular preferencia.

[Etapa 1]

En esta etapa, el compuesto (XXV) se produce al someter el compuesto (XXIV) a una reacción de desprotección. La presente reacción se realiza mediante un método conocido *per se*.

[Etapa 2]

En esta etapa, el compuesto (I-11) se produce al hacer reaccionar el compuesto (XXV) con el compuesto (XXVI). La presente reacción se realiza de la misma manera que en el antes mencionado Método G.

El compuesto (XXIV) que se usa como compuesto de material de partida en el antes mencionado Método R pueden ser producido, por ejemplo, por cualquiera de los antes mencionados Método A a Método L.

Además, el compuesto (XXVI) que se usa como compuesto de material de partida en el antes mencionado Método R se puede producir de acuerdo con un método conocido *per se*.

En cada una de las antes mencionadas reacciones, cuando el compuesto de material de partida tiene un grupo amino, un grupo carboxilo, un grupo hidroxi, un grupo carbonilo o un grupo mercapto como sustituyente, un grupo protector generalmente en la química peptídico y similares se pueden introducir en estos grupos, y el compuesto objeto se puede obtener al eliminar el grupo protector según sea necesario tras la reacción.

El compuesto de la presente invención obtenido por cada método de producción antes mencionado se puede aislar y purificar por medios conocidos tales como concentración, concentración a presión reducida, extracción de solvente, cristalización, recristalización, transferencia de fase, cromatografía y similares. Cada compuesto de material de partida usado en cada uno de los antes mencionados métodos de producción se puede aislar y purificar por un medio conocido similar a los antes mencionados. También, es posible usar dicho compuesto de material de partida como en una mezcla de reacción sin aislamiento, como en el material de partida para la siguiente etapa.

Cuando el compuesto (I) contiene un isómero óptico, un estereoisómero, un isómero de posición o un isómero de rotación, también quedan abarcados en el compuesto (I) y se pueden obtener como productos únicos mediante técnicas de síntesis y técnicas de separación conocidos *per se*. Por ejemplo, cuando el compuesto (I) contiene un isómero óptico, un isómero óptico separado del compuesto también es abarcado por el compuesto (I).

La presente invención se explica en detalle a continuación en referencia a Ejemplos Experimentales, Ejemplos de Referencia, Ejemplos y Ejemplos de Formulación, que no se deben interpretar como limitantes.

Ejemplos

En los siguientes Ejemplos de Referencia y Ejemplos, % significa % en peso a menos que se especifique otra cosa. Además, temperatura ambiente significa una temperatura de 1-30°C a menos que se especifique otra cosa.

Ejemplo de referencia 1

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propionato de etilo (5.21 g) en tetrahidrofurano (12 ml) y etanol (12 ml) se añadió solución acuosa 1 N de hidróxido de sodio (25 ml), y la mezcla se agitó a 50°C durante 30 min. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (25 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (4.15 g, rendimiento: 85%) en forma de agujas delgadas blancas. Punto de fusión 116-117°C.

Ejemplo de referencia 2

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propionato de etilo (4.45 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió solución acuosa 1 N de hidróxido de sodio (21 ml), y

la mezcla se agitó a 50°C durante 40 min. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (21 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar ácido 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propiónico (4,12 g, rendimiento: 99%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.32 (6 H, d, J = 6.0 Hz), 2.54 - 2.69 (2 H, m), 2.73 - 2.83 (2 H, m), 4.38 - 4.59 (1 H, m), 6.63 (1 H, d, J = 2.6 Hz), 6.77 (1 H, dd, J = 8.6, 2.5 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.3 Hz), 8.24 - 8.28 (1 H, m).

Ejemplo de referencia 3

A una solución de 2-hidroxi-4-(metoximetoxi)benzaldehído (74.68 g) en N,N-dimetilformamida (450 ml) se añadió hidruro de sodio (60% en aceite, 19.65 g) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se añadió 2,3-dicloro-5-(trifluorometil)piridina (60.0 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora y a 50°C durante 1 hora. Después de enfriar la mezcla de reacción hasta temperatura helada, se añadió una solución acuosa saturada de cloruro de amonio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera

saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:2, v/v) para dar un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)benzaldehído (79.00 g, rendimiento: 53%) en forma de cristales blancos. Punto de fusión 93.9-94.0°C.

Ejemplo de referencia 4

A una solución de dietilfosfonoacetato de etilo (2.76 g) en tetrahidrofurano (10 ml) se añadió hidruro de sodio (60% en aceite, 482 mg) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se añadió gota a gota una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)benzaldehído (3.90 g) en N,N-dimetilformamida (10 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 35:65, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]acrilato de etilo (4.66 g, rendimiento:

cuant.) en forma de un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 73.5-74.5°C.

Ejemplo de referencia 5

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]acrilato de etilo (52.85 g) en acetona (500 ml) se añadió ácido clorhídrico 1 N (250 ml), y la mezcla se agitó con calentamiento a reflujo durante 5 h. Tras enfriar hasta temperatura ambiente, se añadió una solución acuosa 1 N de hidróxido de sodio (250 ml) a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó dos veces con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]acrilato de etilo (44.52 g, rendimiento: cuant.) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 123.5-124.0°C.

Ejemplo de referencia 6

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]acrilato de etilo (41.68 g) en tetrahidrofurano (1000 ml) se añadieron

tributilfosfina (49.0 ml), 2-metoxietanol (13.0 ml) y 1,1'-azodicarbonildipiperidina (41.01 g), y la mezcla se agitó a 50°C durante 20 min. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilato de etilo (28.67 g, rendimiento: 60%) en forma de cristales en pluma blancos. Punto de fusión 78.2-78.5°C.

Ejemplo de referencia 7

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilato de etilo (2.39 g) en tetrahidrofurano (5.0 ml) y etanol (5.0 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (18.0 ml), y la mezcla se agitó a 50°C durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (18.0 ml) a la mezcla de reacción, y la mezcla se diluyó con tolueno y se concentró. El residuo se disolvió en acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-

[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (1.77 g, rendimiento: 79%) en forma de cristales en pluma blancos. Punto de fusión 156.5-157.5°C.

Ejemplo de referencia 8

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]acrilato de etilo (41.53 g) en N,N-dimetilformamida (10 ml) se añadieron yoduro de 2-propilo (0.65 ml) y carbonato de potasio (712 mg), y la mezcla se agitó a 50°C durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:3, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]acrilato de etilo (1.63 g, rendimiento: 96%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 84.5-85.0°C.

Ejemplo de referencia 9

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]acrilato de etilo (1.53 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (8.0

ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N (8.0 ml) a la mezcla de reacción, y la mezcla se diluyó con tolueno y se concentró. El residuo se disolvió en acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]acrílico (0.91 g, rendimiento: 63%) en forma de un polvo blanco. Punto de fusión 138.0-139.5°C.

Ejemplo de referencia 10

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (4.94 g) en acetato de etilo (100 ml) se añadieron trietilamina (3.50 ml) y cloruro de metansulfonilo (1.40 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en N,N-

dimetilformamida (50 ml) se añadió ftalimida de potasio (2.46 g), y la mezcla se agitó a 80°C durante 3 h. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. El sólido se lavó con éter diisopropílico para dar 2-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}-1H-isoindol-1.3(2H)-diona (6.39 g, rendimiento: 98%). La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 101-103°C.

Ejemplo de referencia 11

A una solución de 2-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}-1H-isoindol-1.3(2H)-diona (6.12 g) en metanol (100 ml) se añadió monohidrato de hidracina (4.02 g), y la mezcla se agitó a 50°C durante 2 h. La mezcla de reacción se concentró, el residuo se lavó con éter dietílico, y el filtrado se concentró. El residuo obtenido se disolvió en éter dietílico, y la capa orgánica se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (2.51 g, rendimiento: 54%) en forma de un aceite marrón oscuro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.51 - 1.95 (4 H, m), 2.40 - 2.55 (2 H, m), 2.68 (2 H, t, J = 7.0 Hz), 3.44 (3 H, s), 3.65 - 3.80 (2 H, m), 4.05 - 4.11(2 H, m), 6.67 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.4, 2.5 Hz), 7.21 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.26 (1 H, d, J = 0.9 Hz).

Ejemplo de referencia 12

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilato de etilo (3.73 g) en tetrahidrofurano (100 ml) se añadió una solución 1.5 M (19.0 ml) de hidruro de diisobutilaluminio en tolueno bajo enfriamiento con hielo, y la mezcla se agitó durante 5 min. Una solución acuosa saturada de cloruro de amonio (5.40 ml) se añadió a la mezcla de reacción, y el sólido precipitado se filtró y el filtrado se concentró para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-ol (3.26 g, rendimiento: 97%) en forma de un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 119-121°C.

Ejemplo de referencia 13

A una solución de 2,4-dihidroxiacetofenona (25.12 g) en tetrahidrofurano (1000 ml) se añadieron trifenilfosfina (70.91 g), 2-metoxietanol (20.0 ml) y una solución de tolueno al 40% de azodicarboxilato de dietilo (120 ml) bajo

enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2.5 h. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar 1-[2-hidroxi-4-(2-metoxietoxi)fenil]etanona (17.96 g, rendimiento: 52%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 2.56 (3 H, s), 3.45 (3 H, s), 3.67 - 3.82 (2 H, m), 4.09 - 4.19 (2 H, m), 6.43 (1 H, d, J = 2.4 Hz), 6.49 (1 H, dd, J = 8.9, 2.4 Hz), 7.63 (1 H, d, J = 9.0 Hz), 12.73 (1 H, s).

Ejemplo de referencia 14

A una solución de 1-[2-hidroxi-4-(2-metoxietoxi)fenil]etanona (5.08 g) en N,N-dimetilformamida (50 ml) se añadieron carbonato de potasio (4.71 g) y bromuro de bencilo (3.50 ml), y la mezcla se agitó a temperatura ambiente durante 3 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar 1-[2-(benciloxi)-4-(2-metoxietoxi)fenil]etanona (7.00 g, rendimiento: 97%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 2.55 (3 H, s), 3.45 (3 H, s), 3.65 - 3.79 (2 H, m), 4.09 - 4.20 (2 H, m), 5.13 (2 H, s),

6.45 - 6.70 (2 H, m), 7.32 - 7.51 (5 H, m), 7.84 (1 H, d, J = 8.7 Hz).

Ejemplo de referencia 15

A una solución de dietilfosfonoacetato de etilo (7.34 g) en etanol (45 ml) se añadió etóxido de sodio (1.93 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 20 min. A la mezcla de reacción se añadió una solución de 1-[2-(benciloxi)-4-(2-metoxietoxi)fenil]etanona (7.00 g) en etanol (45 ml), y la mezcla se agitó con calentamiento a reflujo durante 20 h. Tras enfriar hasta temperatura ambiente, se agregó una solución acuosa saturada de cloruro de amonio, y la mezcla se diluyó con tolueno y se concentró. El residuo se disolvió en acetato de etilo, y la capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 35:65, v/v) para dar (2E)-3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]-2-butenoato de etilo (Ejemplo de referencia 15a: 6.17 g, rendimiento: 72%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.29 (3 H, t, J = 7.1 Hz), 2.50 (3 H, d, J = 1.3 Hz), 3.45 (3 H, s), 3.70 - 3.78 (2 H, m), 4.06 - 4.13 (2 H, m), 4.19 (2 H, q, J = 7.2 Hz), 5.05 (2 H, s), 5.93 (1 H, d, J = 1.3 Hz), 6.48 (1 H, dd, J = 8.4, 2.4 Hz), 6.59 (1 H, d, J = 2.3 Hz), 7.11 (1 H, d, J = 8.3 Hz),

7.28 - 7.46 (5 H, m).

Luego se obtuvo (2Z)-3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]-2-butenoato de etilo (Ejemplo de referencia 15b: 1.90 g, rendimiento: 22%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.06 (3 H, t, J = 7.1 Hz), 2.15 (3 H, d, J = 1.3 Hz), 3.44 (3 H, s), 3.66 - 3.79 (2 H, m), 3.96 (2 H, q, J = 7.0 Hz), 4.06 - 4.14 (2 H, m), 5.03 (2 H, s), 5.93 (1 H, d, J = 1.5 Hz), 6.50 (1 H, dd, J = 8.4, 2.4 Hz), 6.58 (1 H, d, J = 2.3 Hz), 6.96 (1 H, d, J = 8.3 Hz), 7.29 - 7.40 (5 H, m).

Ejemplo de referencia 16

A una solución de (2E)-3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]-2-butenoato de etilo (6.17 g) en tetrahidrofurano (20 ml) y etanol (20 ml) se añadió paladio sobre carbón al 10% (1.91 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró y el filtrado se concentró para dar 3-[2-hidroxi-4-(2-metoxietoxi)fenil]butanoato de etilo (4.36 g, rendimiento: 93%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.19 (3 H, t, J = 7.2 Hz), 1.30 (3 H, d, J = 7.2 Hz), 2.49 - 2.70 (2 H, m), 3.44 (3 H, s), 3.45 - 3.56 (1 H, m), 3.70 - 3.74 (2 H, m), 4.00 - 4.16 (4 H, m), 6.45 - 6.49 (1 H, m), 6.50 - 6.59 (1 H, m), 6.93 (1 H, s), 7.04 (1 H, d, J = 8.5 Hz).

Ejemplo de referencia 17

A una solución de 3-[2-hidroxi-4-(2-metoxietoxi)fenil]butanoato de etilo (5.50 g) en N,N-dimetilformamida (40 ml) se añadió hidruro de sodio (60% en aceite, 932 mg) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se agregó 2.3-dicloro-5-(trifluorometil)piridina (3.0 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 35:65, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoato de etilo (7.80 g, rendimiento: 87%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.16 (3 H, t, J = 7.2 Hz), 1.22 (3 H, d, J = 7.0 Hz), 2.39 - 2.50 (1 H, m), 2.56 - 2.70 (1 H, m), 3.23 - 3.38 (1 H, m), 3.43 (3 H, s), 3.65 - 3.79 (2 H, m), 3.96 - 4.19 (4 H, m), 6.66 (1 H, d, J = 2.6 Hz), 6.85 (1 H, dd, J = 8.7, 2.6 Hz), 7.18 - 7.29 (1 H, m), 7.98 (1 H, d, J = 2.1 Hz), 8.25 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 18

A una solución de 3-[2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoato de etilo (7.80 g) en tetrahidrofurano (45 ml) se añadió se añadió una solución en hexano 1.0 M de hidruro de diisobutilaluminio (80.0 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1 hora. Una solución acuosa saturada de cloruro de amonio (15.0 ml) se añadió a la mezcla de reacción, y la mezcla se agitó durante 1 hora. El sólido precipitado se filtró y el filtrado se concentró para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butan-1-ol (7.46 g, rendimiento: cuant.) en forma de un aceite anaranjado.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.20 (3 H, d, J = 7.0 Hz), 1.62 (1 H, t, J = 6.0 Hz), 1.75 - 1.87 (2 H, m), 2.90 - 3.05 (1 H, m), 3.43 (3 H, s), 3.50 (2 H, q, J = 5.9 Hz), 3.68 - 3.77 (2 H, m), 3.90 - 4.24 (2 H, m), 6.61 (1 H, d, J = 2.6 Hz), 6.89 (1 H, dd, J = 8.7, 2.6 Hz), 7.09 - 7.34 (1 H, m), 7.99 (1 H, d, J = 1.7 Hz), 8.25 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo de referencia 19

A una solución de 2-fosfonopropionato de trietilo (7.93 g) en tetrahidrofurano (30 ml) se añadió hidruro de sodio (60% en aceite, 1.31 g) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se añadió gota a gota una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)benzaldehído

(10.01 g) en N,N-dimetilformamida (30 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (1:4 - 1:2, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]-2-metilacrilato de etilo (13.71 g, rendimiento: cuant.) en forma de un aceite de color amarillo pálido (E/Z = 10:1.5).

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.25 (3 H, t, J = 7.2 Hz), 2.01 (3 H, d, J = 1.5 Hz), 3.50 (3 H, s), 4.17 (2 H, q, J = 7.2 Hz), 5.20 (2 H, s), 6.92 (1 H, d, J = 2.4 Hz), 7.01 (1 H, dd, J = 8.7, 2.4 Hz), 7.38 (1 H, d, J = 8.5 Hz), 7.49 (1 H, s), 7.96 (1 H, d, J = 1.9 Hz), 8.23 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 20

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]-2-metilacrilato de etilo (13.71 g) en acetona (150 ml) se añadió ácido clorhídrico 1 N (60 ml), y la mezcla se agitó durante la noche a 50°C. Tras enfriar hasta temperatura ambiente, se añadió una solución acuosa 1 N de hidróxido de sodio (60 ml) a

la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]-2-metilacrilato de etilo (10.13 g, rendimiento: 91%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 101.5-102.0°C.

Ejemplo de referencia 21

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]-2-metilacrilato de etilo (4.96 g) en tetrahidrofurano (100 ml) se añadieron tributilfosfina (6.00 ml), 2-metoxietanol (1.50 ml) y 1.1'-azodicarbonildipiperidina (4.51 g), y la mezcla se agitó a 50°C durante 30 min. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrilato de etilo (5.38 g, rendimiento: 95%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.23 - 1.29 (3 H, m), 2.02

(3 H, d, J = 1.5 Hz), 3.45 (3 H, s), 3.73 - 3.80 (2 H, m), 4.06 - 4.23 (4 H, m), 6.78 (1 H, d, J = 2.6 Hz), 6.91 (1 H, dd, J = 8.7, 2.4 Hz), 7.39 (1 H, d, J = 8.7 Hz), 7.50 (1 H, s), 7.96 (1 H, d, J = 2.1 Hz), 8.22 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 22

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrilato de etilo (1.76 g) en tetrahidrofurano (40 ml) se añadió paladio sobre carbón al 10% (1.91 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró. Una solución hexanólica 1.0 M de hidruro de diisobutilaluminio (16.0 ml) se añadió al filtrado bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente. Al cabo de 1 hora, se añadió una solución hexanólica 1.0 M de hidruro de diisobutilaluminio (14.0 ml) a temperatura ambiente, y la mezcla se agitó durante 1 hora. Una solución acuosa saturada de cloruro de amonio (5.70 ml) se añadió a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. El sólido precipitado se filtró y el filtrado se concentró para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilpropan-1-ol (1.41 g, rendimiento: 88%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 84-86°C.

Ejemplo de referencia 23

A una solución de 3-(2-hidroxi-4-isopropoxifenil)propionato de etilo (10.0 g) en N,N-dimetilformamida (150 ml) se añadió hidruro de sodio (60% en aceite, 1.92 g) a temperatura ambiente, y la mezcla se agitó durante 30 min. Se agregó cloruro de 2,4-diclorobencilo (6.7 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró.

El residuo obtenido se disolvió en tetrahidrofurano (300 ml), se añadió hidruro de litio y aluminio (1.52 g) a temperatura ambiente, y la mezcla se agitó durante 30 min. Se agregó sulfato de sodio decahidratado (12.9 g) a la mezcla de reacción, y el sólido resultante se filtró y el filtrado se concentró. La recristalización del sólido residual en acetato de etilo-hexano dio 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}propan-1-ol (11.2 g, rendimiento: 76%) en forma de agujas incoloras. Punto de fusión 75.5-76.5°C.

Ejemplo de referencia 24

A una solución de 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}propan-1-ol (2.54 g) en diclorometano (20 ml) se añadió reactivo de Dess-Martin (3.21 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante

30 min. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar un 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}propanal (2.88 g, rendimiento: cuant.) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.22 - 1.39 (6 H, m), 2.67 - 2.83 (2 H, m), 2.94 (2 H, t, J = 7.4 Hz), 4.33 - 4.60 (1 H, m), 5.08 (2 H, s), 6.41 - 6.54 (1 H, m), 7.05 (1 H, d, J = 8.7 Hz), 7.29 (1 H, dd, J = 8.3, 2.1 Hz), 7.39 - 7.50 (1 H, m), 7.65 - 7.78 (1 H, m), 7.84 - 8.07 (2 H, m), 8.27 (1 H, dd, J = 7.6, 1.2 Hz), 9.79 (1 H, t, J = 1.7 Hz).

Ejemplo de referencia 25

A una solución de 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}propanal (2.88 g) en tetrahidrofurano (12 ml), ter-butanol (12 ml) y agua (12 ml) se añadieron dihidrógeno-fosfato de sodio (0.91 g), clorito de sodio (1.90 g) y 2-metil-2-buteno (4.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. La recristalización

del residuo obtenido en acetato de etilo-hexano y el lavado con éter diisopropílico dio ácido 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}propiónico (1.03 g, rendimiento: 39%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.30 - 1.34 (6 H, m), 2.61 - 2.71 (2 H, m), 2.95 (2 H, t, J = 7.7 Hz), 4.41 - 4.56 (1 H, m), 5.06 - 5.13 (2 H, m), 6.40 - 6.49 (2 H, m), 7.08 (1 H, d, J = 8.5 Hz), 7.29 (1 H, dd, J = 8.4, 2.2 Hz), 7.42 (1 H, d, J = 2.1 Hz), 7.50 (1 H, d, J = 8.3 Hz).

Ejemplo de referencia 26

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propionato de etilo (27.52 g) en tetrahidrofurano (320 ml) se añadió ácido clorhídrico concentrado (10.0 ml), y la mezcla se agitó a 50°C durante 45 min. Tras enfriar hasta temperatura ambiente, se añadió una solución acuosa 1 N de hidróxido de sodio (120 ml) a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]propionato de etilo (20.54 g, rendimiento: 83%)

en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.09 - 1.38 (3 H, m), 2.44 - 2.68 (2 H, m), 2.68 - 2.85 (2 H, m), 3.97 - 4.25 (2 H, m), 6.61 (1 H, d, J = 2.2 Hz), 6.65 - 6.77 (1 H, m), 7.18 (1 H, d, J = 8.1 Hz), 7.98 (1 H, d, J = 2.2 Hz), 8.26 (1 H, s).

Ejemplo de referencia 27

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]propionato de etilo (0.68 g) en N,N-dimetilformamida (15 ml) se añadieron carbonato de potasio (321.5 mg) y 2-cloro-N,N-dietilacetamida (0.31 g), y la mezcla se agitó a temperatura ambiente durante 2 h, a 50°C durante 30 min y a 80°C durante 1 hora. Se agregó 2-cloro-N,N-dietilacetamida (0.30 g), y la mezcla se siguió agitando durante 30 min. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:2, v/v) para dar 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}propionato de etilo (1.39 g, rendimiento: cuant.) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales de algodón blanco. Punto

de fusión 88.5-89.0°C.

Ejemplo de referencia 28

A una solución de 1-bromo-3-metoxipropano (19.50 g) en N,N-dimetilformamida (200 ml) se añadió tioacetato de potasio (15.15 g), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con éter dietílico. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite amarillo.

A una solución del aceite obtenido en éter dietílico (200 ml) se añadió solución acuosa 1 N de hidróxido de sodio (250 ml) bajo enfriamiento con hielo, y la mezcla se agitó bajo enfriamiento con hielo. Al cabo de 1 hora, se añadieron una solución acuosa 12 N de hidróxido de sodio (20 ml) y metanol (50 ml), y la mezcla se agitó a temperatura ambiente durante 20 min. Se agregó ácido clorhídrico concentrado (45 ml) a la mezcla de reacción, y la mezcla se extrajo con éter dietílico. La capa orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró.

En una solución del residuo obtenido en ácido acético (200 ml) y agua (200 ml) se introdujo cloro gaseoso durante 2 horas, para que la temperatura en el sistema no se elevara a 15°C o más. El nitrógeno gaseoso se introdujo en a temperatura ambiente durante 1 h, la mezcla de reacción se

añadió gota a gota a una solución acuosa saturada de carbonato ácido de sodio enfriada con hielo, y la mezcla se extrajo con éter dietílico. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio, una solución acuosa al 10% de tiosulfato de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite de color amarillo pálido.

Una solución del aceite obtenido en tetrahidrofurano (10 ml) se añadió gota a gota a una solución de amonio acuoso al 28% (50 ml) y tetrahidrofurano (50 ml) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite anaranjado. El aceite obtenido se disolvió en una suspensión de carbón activado en acetato de etilo, y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla se filtró y se concentró para dar 3-metoxipropano-1-sulfonamida (0.88 g, rendimiento: 5%) en forma de un sólido anaranjado.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.86 - 2.25 (2 H, m), 3.19 - 3.28 (2 H, m), 3.35 (3 H, s), 3.53 (2 H, t, J = 5.8 Hz), 4.71 (2 H, s).

Ejemplo de referencia 29

A una solución de (2E)-3-[2-(benciloxi)-4-

hidroxifenil]acrilato de etilo (2.01 g) en tetrahidrofurano (100 ml) se añadieron trifenilfosfina (2.65 g), 1-(2-hidroxietil)-2-pirrolidona (0.80 ml) y una solución toluénica al 40% de azodicarboxilato de dietilo (5.50 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:3 acetato de etilo solo, v/v), luego acetato de etilo-metanol (acetato de etilo solo a 9:1, v/v) para dar (2E)-3-{2-(benciloxi)-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}acrilato de etilo (4.01 g, rendimiento: cuant.) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 94-97°C.

Ejemplo de referencia 30

A una solución de acrilato de (2E)-3-{2-(benciloxi)-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}etilo (3.81 g) en tetrahidrofurano (25 ml) y etanol (25 ml) se añadió paladio sobre carbón al 10% (1.00 g), y la mezcla se agitó durante la noche bajo una atmósfera de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró y el filtrado se concentró para dar 3-{2-hidroxi-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}propionato de etilo (3.05 g, rendimiento: cuant.) en forma de un sólido de color marrón pálido. La recristalización en acetato de etilo-éter diisopropílico dio

un polvo blanco. Punto de fusión 112-115°C.

Ejemplo de referencia 31

A una solución de 3-{2-hidroxi-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}propionato de etilo (2.90 g) en N,N-dimetilformamida (50 ml) se añadió hidruro de sodio (60% en aceite, 464 mg) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se agregó 2.3-dicloro-5-(trifluorometil)piridina (1.50 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1 acetato de etilo solo, v/v) para dar un aceite anaranjado.

A una solución del aceite obtenido en tetrahidrofurano (15 ml) y etanol (15 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (16.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió una solución acuosa 1 N de hidróxido de sodio (15.0 ml) y, al cabo de 1 h, también se agregó una solución acuosa 1 N de hidróxido de sodio (10.0 ml), y la mezcla se agitó durante 1 hora. Se añadió ácido clorhídrico 1 N (41.0 ml) a la mezcla de reacción, y la mezcla se concentró. El residuo se disolvió

en acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 acetato de etilo solo, v/v), luego acetato de etilo-metanol (acetato de etilo solo a 9:1, v/v), para dar ácido 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}propiónico (0.85 g, 27%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio un polvo blanco. Punto de fusión 145.0-145.5°C.

Ejemplo de referencia 32

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil]propionato de etilo (3.26 g) en diclorometano (40 ml) se añadieron 2.6-lutidina (2.0 ml) y trifluorometansulfonato de triisopropilsililo (2.50 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Bajo enfriamiento con hielo, también se añadieron 2,6-lutidina (2.0 ml) y trifluorometansulfonato de triisopropilsililo (2.50 ml), y la mezcla se agitó durante 15 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró.

El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 35:65, v/v) para dar un aceite amarillo.

A una solución del aceite obtenido en tetrahidrofurano (40 ml) se añadió solución toluénica 1.5 M de hidruro de diisobutilaluminio (20.0 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 15 min. Una solución acuosa saturada de cloruro de amonio (5.80 ml) se añadió a la mezcla de reacción, y el sólido precipitado se filtró y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v) para dar un aceite amarillo.

A una solución del aceite obtenido en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (345 mg), y la mezcla se agitó a 40°C durante 1 hora. Se agregó ciclopropilmetilamina (834 mg) a la mezcla de reacción, y la mezcla se agitó a 50°C durante 5 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite anaranjado.

A una solución del aceite obtenido en

tetrahidrofurano (4 ml) se añadió solución 1.0 M en tetrahidrofurano de fluoruro de tetrabutilamonio (4.0 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar (ciclopropilmetil)carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propilo (749 mg, rendimiento: 39%) en forma de un aceite de color anaranjado pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.11 - 0.25 (2 H, m), 0.41 - 0.56 (2 H, m), 0.72 - 1.19 (1 H, m), 1.78 - 1.95 (2 H, m), 2.50 (2 H, t, J = 7.5 Hz), 2.95 - 3.07 (2 H, m), 4.02 (2 H, t, J = 6.1 Hz), 4.71 (1 H, s), 6.58 - 6.63 (1 H, m), 6.67 - 6.79 (1 H, m), 7.12 - 7.19 (1 H, m), 7.98 (1 H, d, J = 2.3 Hz), 8.27 (1 H, dd, J = 2.0, 1.0 Hz).

Ejemplo de referencia 33

A una solución de 2,4-dihidroxibenzaldehído (25.29 g) en tetrahidrofurano (1000 ml) se añadieron trifenilfosfina (70.34 g), 2-metoxietanol (20.0 ml) y una solución toluénica al 40% de azodicarboxilato de dietilo (120 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante la noche

a temperatura ambiente. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 2-hidroxi-4-(2-metoxietoxi)benzaldehído (12.65 g, rendimiento: 35%) en forma de agujas finas blancas. Punto de fusión 64.5-65.5°C.

Ejemplo de referencia 34

A una solución de 2-hidroxi-4-(2-metoxietoxi)benzaldehído (12.86 g) en N,N-dimetilformamida (100 ml) se añadió hidruro de sodio (60% en aceite, 3.24 g) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se añadió 2.3-dicloro-5-(trifluorometil)piridina (12.0 ml), y la mezcla se agitó a temperatura ambiente durante 3 horas y a 50°C durante 30 min. Después de enfriar la mezcla de reacción hasta temperatura ambiente, se añadió una solución acuosa saturada de cloruro de amonio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v). Se suspendió el carbón activado en la fracción eluida, y la suspensión se agitó durante 1 hora, se filtró y se concentró para dar 2-{[3-cloro-5-(trifluorometil)piridin-2-

il]oxi}-4-(2-metoxietoxi)benzaldehído (14.66 g, rendimiento: 60%) en forma de un polvo amarillo pálido. La recristalización en acetato de etilo-hexano dio un prisma blanco. Punto de fusión 80.5-81.0°C.

Ejemplo de referencia 35

A una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)benzaldehído (13.04 g) en tetrahidrofurano (50 ml) y metanol (30 ml) se añadió borohidruro de sodio (3.99 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1 hora. También, se añadió borohidruro de sodio (1.21 g), y la mezcla se agitó durante 1 hora. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v) y luego en cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (1:1 acetato de etilo solo, v/v) para dar [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (2.51 g, rendimiento: 19%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 85.0-85.5°C.

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Ejemplo de referencia 36

A una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoximetoxi)benzaldehído (26.42 g) en tetrahidrofurano (500 ml) se añadió ácido clorhídrico concentrado (50.0 ml), y la mezcla se agitó a temperatura ambiente durante 17 h. Una solución acuosa 1 N de hidróxido de sodio (600 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:2, v/v) para dar una 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxibenzaldehído (22.63 g, rendimiento: 98%) en forma de un sólido rosado pálido. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 129°C (desc.).

Ejemplo de referencia 37

A una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxibenzaldehído (3.12 g) en N,N-dimetilformamida (20 ml) se añadió carbonato de potasio (2.25 g) y 1-yodobutano (1.50 ml), y la mezcla se agitó a 50°C durante 1 hora. Después de enfriar, la mezcla de reacción hasta temperatura ambiente, la mezcla se extrajo con una solución acuosa saturada de cloruro de amonio y acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada,

se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en tetrahidrofurano (15 ml) y metanol (15 ml) se añadió borohidruro de sodio (895 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El concentrado se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar (4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)metanol (2.76 g, rendimiento: 75%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio agujas finas blancas. Punto de fusión 77.8-79.2°C.

Ejemplo de referencia 38

A una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxibenzaldehído (3.09 g) en N,N-dimetilformamida (20 ml) se añadió carbonato de potasio (2.08 g) y 2-yodopropano (1.50 ml), y la mezcla se agitó a 50°C durante 1.5 h. Después de enfriar, la mezcla de

reacción hasta temperatura ambiente, la mezcla se extrajo con una solución acuosa saturada de cloruro de amonio y acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55, v/v) para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en tetrahidrofurano (15 ml) y metanol (15 ml) se añadió borohidruro de sodio (912 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El concentrado se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar (2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)metanol (2.48 g, rendimiento: 71%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio un polvo blanco. Punto de fusión 63.0-64.0°C.

Ejemplo de referencia 39

A una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxibenzaldehído (3.09

g) en tetrahidrofurano (50 ml) se añadieron piridina (5.0 ml) y cloruro de 1-propansulfonilo (1.60 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Luego se añadieron trietilamina (5.0 ml), cloruro de 1-propansulfonilo (1.60 ml) y acetato de etilo (50 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un aceite amarillo.

A una solución del aceite obtenido en metanol (30 ml) se añadió borohidruro de sodio (385.1 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 20 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El concentrado se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (1:9 - 3:2, v/v) para dar propan-1-sulfonato de 3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(hidroximetil)fenilo (2.44 g, rendimiento: 59%) en

forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 68.5-69.5°C.

Ejemplo de referencia 40

Una solución de sulfamida (811 mg) y N-metilhexilamina (1.00 ml) en 1,2-dimetoxietano (25 ml) se agitó durante la noche con calentamiento a reflujo. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar N-hexil-N-metilsulfamida (0.67 g, rendimiento: 52%) en forma de un sólido de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.80 - 0.96 (3 H, m), 1.10 - 1.43 (6 H, m), 1.46 - 1.62 (2 H, m), 2.80 (3 H, s), 2.98 - 3.17 (2 H, m), 4.56 (2 H, s).

Ejemplo de referencia 41

A una solución de 2-hidroxi-4-(2-metoxietoxi)benzaldehído (9.30 g) en N,N-dimetilformamida (100 ml) se añadieron carbonato de potasio (6.91 g) y bromuro de bencilo (7.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica

se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 2-(benciloxi)-4-(2-metoxietoxi)benzaldehído (10.71 g, rendimiento: 79%) en forma de cristales blancos. Punto de fusión 67.5-68.0°C.

Ejemplo de referencia 42

A una solución de bromuro de [2-(1,3-dioxolan-2-il)etil]trifenilfosfonio (6.96 g) en N,N-dimetilformamida (50 ml) se añadió hidruro de sodio (60% en aceite, 628 mg) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego una solución de 2-(benciloxi)-4-(2-metoxietoxi)benzaldehído (3.12 g) en N,N-dimetilformamida (30 ml) se añadió gota a gota, y la mezcla se agitó a temperatura ambiente durante 1 hora y a 80°C durante 5 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un aceite incoloro.

A una solución del aceite obtenido en etanol (50 ml)

se añadió paladio sobre carbón al 10% (3.16 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar 2-[3-(1,3-dioxolan-2-il)propil]-5-(2-metoxietoxi)fenol (0.93 g, rendimiento: 30%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.64 - 1.87 (4 H, m), 2.61 (2 H, t, J = 6.8 Hz), 3.44 (3 H, s), 3.64 - 3.77 (2 H, m), 3.84 - 3.94 (2 H, m), 3.94 - 4.26 (4 H, m), 4.91 (1 H, t, J = 4.3 Hz), 6.22 (1 H, s), 6.33 - 6.62 (2 H, m), 6.96 (1 H, d, J = 8.1 Hz).

Ejemplo de referencia 43

A una solución de 2-[3-(1,3-dioxolan-2-il)propil]-5-(2-metoxietoxi)fenol (0.93 g) en N,N-dimetilformamida (10 ml) se añadió hidruro de sodio (60% en aceite, 155 mg) bajo enfriamiento con hielo, y la mezcla se agitó posteriormente durante 30 min. Luego se añadió 2.3-dicloro-5-(trifluorometil)piridina (0.50 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a

cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar 3-cloro-2-[2-[3-(1,3-dioxolan-2-il)propil]-5-(2-metoxietoxi)fenoxi]-5-(trifluorometil)piridina (1.33 g, rendimiento: 87%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio un polvo blanco. Punto de fusión 92.0-92.5°C.

Ejemplo de referencia 44

Una solución de 3-cloro-2-[2-[3-(1,3-dioxolan-2-il)propil]-5-(2-metoxietoxi)fenoxi]-5-(trifluorometil)piridina (1.08 g) en una solución acuosa al 80% de ácido acético (15 ml) se agitó a 50°C durante 4 horas y a 80°C durante 3 h. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en ter-butanol (10 ml) y agua (2.5 ml) se añadieron dihidrógeno-fosfato de sodio (313 mg), clorito de sodio (645 mg) y 2-metil-2-buteno (4.5 ml) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 30 min., una solución acuosa al 10% de hidrógeno-sulfito de sodio y ácido clorhídrico 1 N se añadieron a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. La recristalización del residuo obtenido en acetato de etilo-

hexano dio ácido 4-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoico (612 mg, rendimiento: 60%) en forma de agujas finas blancas. Punto de fusión 119.0-119.5°C.

Ejemplo de referencia 45

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butan-1-ol (2.63 g) en diclorometano (30 ml) se añadió a reactivo de Dess-Martin (3.46 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 10 min. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en tetrahidrofurano (30 ml), ter-butanol (24 ml) y agua (6 ml) se añadieron dihidrógeno-fosfato de sodio (803 mg), clorito de sodio (601 mg) y 2-metil-2-buteno (6.5 ml) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 20 min. Se añadieron una solución acuosa al 10% de hidrógeno-sulfito de sodio y ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa

orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 7:3, v/v) para dar ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoico (2.51 g, rendimiento: 92%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.25 (3 H, d, J = 6.8 Hz), 2.44 - 2.54 (1 H, m), 2.61 - 2.81 (1 H, m), 3.27 - 3.39 (1 H, m), 3.43 (3 H, s), 3.65 - 3.78 (2 H, m), 3.99 - 4.14 (2 H, m), 6.65 (1 H, d, J = 2.6 Hz), 6.85 (1 H, dd, J = 8.7, 2.4 Hz), 7.12 - 7.24 (1 H, m), 7.98 (1 H, d, J = 2.3 Hz), 8.22 - 8.28 (1 H, m).

Ejemplo de referencia 46

Una mezcla de 3-[1-(2,4-difluorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoato de etilo (0.16 g), una solución acuosa 1 N de hidróxido de sodio (4.0 ml), tetrahidrofurano (4.0 ml) y etanol (4.0 ml) se agitó a 60°C durante 30 min, se añadió ácido clorhídrico 1 N (20 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar ácido 3-[1-(2,4-difluorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (140 mg, rendimiento: 95%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.3 Hz),

2.63 (2 H, t, J = 7.4 Hz), 2.83 (2 H, t, J = 7.4 Hz), 4.62 - 4.74 (1 H, m), 5.13 (2 H, s), 5.49 (1 H, s), 6.74 - 6.98 (3 H, m).

Ejemplo de referencia 47

Una solución mixta de 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoato de etilo (4.00 g), una solución acuosa 1 N de hidróxido de sodio (18 ml), tetrahidrofurano (20 ml) y metanol (20 ml) se agitó a 50°C durante 2 h. Se añadieron ácido clorhídrico 1 N (19 ml) y salmuera (30 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (60 mlx2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. Los cristales crudos obtenidos se recristalizaron en hexano-acetato de etilo para dar ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (3.54 g, rendimiento: 82%) en forma de cristales incoloros. Punto de fusión 114-115°C.

Ejemplo de referencia 48

Una mezcla de 3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]propanoato de etilo (1.00 g), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (20 ml) y etanol (20 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (30 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se

secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]propanoico (680 mg, rendimiento: 74%) en forma de cristales incoloros. Punto de fusión 105-108°C.

Ejemplo de referencia 49

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]acrilato de etilo (950 mg), una solución acuosa 1 N de hidróxido de sodio (8.0 ml), tetrahidrofurano (20 ml) y etanol (20 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (30 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]acrílico (790 mg, rendimiento: 90%) en forma de cristales incoloros. Punto de fusión 170-171°C.

Ejemplo de referencia 50

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]acrilato de etilo (600 mg), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (15 ml) y etanol (15 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (30 ml), y la mezcla se extrajo con

acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]acrílico (420 mg, rendimiento: 75%) en forma de cristales incoloros. Punto de fusión 174-175°C.

Ejemplo de referencia 51

Una mezcla de 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}propanoato de etilo (1.90 g), una solución acuosa 1 N de hidróxido de sodio (10 ml), tetrahidrofurano (30 ml) y etanol (30 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}propanoico (1.20 g, rendimiento: 68%) en forma de cristales incoloros. Punto de fusión 117-119°C.

Ejemplo de referencia 52

Una mezcla de 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoato de etilo (2.07 g), una solución acuosa 1 N de hidróxido de sodio (13 ml), tetrahidrofurano (30 ml) y etanol (30 ml) se agitó a 50°C durante 1 hora. La mezcla de

reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoico (1.70 g, rendimiento: 88%) en forma de cristales incoloros. Punto de fusión 123-124°C.

Ejemplo de referencia 53

Una mezcla de 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrilato de etilo (4.00 g), una solución acuosa 1 N de hidróxido de sodio (20 ml), tetrahidrofurano (40 ml) y etanol (40 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrílico (2.82 g, rendimiento: 76%) en forma de cristales incoloros. Punto de fusión 176-179°C.

Ejemplo de referencia 54

A una mezcla de ter-butóxido de potasio (132 g) y tetrahidrofurano (600 ml) se añadió gota a gota una mezcla de acetofenona (100 g) y oxalato de dietilo (123 g), y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron ácido acético (119 ml) y monohidrato de hidracina (45.8 g) a

la mezcla de reacción, y la mezcla se agitó con calentamiento a reflujo durante 2 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con solución acuosa saturada de carbonado de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en éter diisopropílico para dar 3-fenil-1H-pirazol-5-carboxilato de etilo (145 g, rendimiento: 81%) en forma de un sólido marrón.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.36 (3 H, t, J = 7.2 Hz), 4.36 (2 H, q, J = 7.2 Hz), 7.10 (1 H, s), 7.30 - 7.46 (3 H, m), 7.71 - 7.80 (2 H, m), 11.86 (1 H, brs).

Ejemplo de referencia 55

Una mezcla de 3-fenil-1H-pirazol-5-carboxilato de etilo (70.0 g), cloruro de 2,4-diclorobencilo (69.6 g), carbonato de potasio (53.7 g) y N,N-dimetilformamida (400 ml) se agitó a temperatura ambiente durante 15 h, la mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-carboxilato de etilo (61.0 g, rendimiento: 50%) en forma de cristales marrones. Punto de fusión 104-107°C.

Ejemplo de referencia 56

A una solución de 1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-carboxilato de etilo (60.0 g) en tetrahidrofurano (400 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (267 ml) a 0°C. La mezcla se agitó a temperatura ambiente durante 2 horas y se añadió metanol para neutralizar la reacción. La mezcla de reacción se vertió en una solución acuosa al 10% de sal de Rochelle, y la mezcla se agitó y se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar [1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]metanol (48.9 g, rendimiento: 92%) en forma de cristales de color marrón pálido. Punto de fusión 140-141°C.

Ejemplo de referencia 57

Bajo una atmósfera de nitrógeno, a una solución de cloruro de oxalilo (15.2 g) en diclorometano (100 ml) se añadió dimetilsulfóxido (28.1 g) a -78°C, y la mezcla se agitó durante 5 min. Se agregó una solución de [1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]metanol (20.0 g) en diclorometano (300 ml). Tras agitar a -78°C durante 1 hora, se añadió trietilamina (30.3 g), y la mezcla de reacción se calentó hasta temperatura ambiente y luego se agitó durante 1 h. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se

lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-carbaldehído (13.3 g, rendimiento: 67%) en forma de cristales de color amarillo pálido. Punto de fusión 135-137°C.

Ejemplo de referencia 58

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (10.2 g) en N,N-dimetilformamida (50 ml) se añadió hidruro de sodio (60% en aceite, 1.57 g), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 1-[2,4-diclorobencil]-3-fenil-1H-pirazol-5-carbaldehído (10.0 g) en tetrahidrofurano (60 ml), y la mezcla se agitó durante 1 hora. Una solución acuosa saturada de cloruro de amonio se añadió para neutralizar la reacción. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]acrilato de etilo (11.5 g, rendimiento: 95%) en forma de cristales incoloros. Punto de fusión 123-124°C.

Ejemplo de referencia 59

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]acrilato de etilo (7.00 g), paladio-carbón al

5% (860 mg) y tetrahidrofurano (100 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]propanoato de etilo (4.18 g, rendimiento: 60%) en forma de cristales incoloros. Punto de fusión 91-93°C.

Ejemplo de referencia 60

Una mezcla de 3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]propanoato de etilo (5.22 g), una solución acuosa 1 N de hidróxido de sodio (20 ml), tetrahidrofurano (50 ml) y etanol (50 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]propanoico (4.28 g, rendimiento: 88%) en forma de cristales incoloros. Punto de fusión 160-161°C.

Ejemplo de referencia 61

A una solución de 3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]propanoato de etilo (2.00 g), 2-metoxietanol (887 mg) y tributilfosfina (2.37 g) en tetrahidrofurano (150 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (2.95 g), y la mezcla se agitó a

temperatura ambiente durante 15 horas y se concentró. Se añadió éter diisopropílico al residuo, el material insoluble restante se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:1, v/v) para dar 3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]propanoato de etilo (1.70 g, rendimiento: 73%) en forma de un aceite incoloro.

Una mezcla de 3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]propanoato de etilo (1.70 g), una solución acuosa 1 N de hidróxido de sodio (10 ml), tetrahidrofurano (25 ml) y etanol (25 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]propanoico (1.48 g, rendimiento: 94%) en forma de cristales incoloros. Punto de fusión 111-113°C.

Ejemplo de referencia 62

A una solución de 3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]propanoato de etilo (1.00 g), alcohol bencílico (630 mg) y tributilfosfina (1.18 g) en tetrahidrofurano (70 ml) se añadió 1.1'-

(azodicarbonil)dipiperidina (1.47 g), y la mezcla se agitó a temperatura ambiente durante 15 horas y se concentró. Se añadió éter diisopropílico al residuo, el material insoluble restante se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v) para dar 3-[3-(benciloxi)-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoato de etilo (510 mg, rendimiento: 40%) en forma de un aceite incoloro.

Una mezcla de 3-[3-(benciloxi)-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoato de etilo (510 mg), una solución acuosa 1 N de hidróxido de sodio (3.0 ml), tetrahidrofurano (8.0 ml) y etanol (8.0 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[3-(benciloxi)-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoico (420 mg, rendimiento: 88%) en forma de cristales incoloros. Punto de fusión 98-101°C.

Ejemplo de referencia 63

Una mezcla de 3-hidroxipirazol-5-carboxilato de metilo (48.2 g), carbonato de potasio (51.6 g), 1-yodobutano (40.5 g) y N,N-dimetilformamida (300 ml) se agitó a

temperatura ambiente durante 12 h. La mezcla de reacción se concentró, y el concentrado se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en hexano para dar 3-butoxipirazol-5-carboxilato de metilo (43.6 g, rendimiento: 64%, que contiene isómero en aproximadamente el 10%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.41 - 1.54 (2 H, m), 1.71 - 1.81 (2 H, m), 3.91 (3 H, s), 4.16 (2 H, t, J = 6.6 Hz), 6.21 (1 H, s), 9.90 - 10.20 (1 H, brs).

Ejemplo de referencia 64

Una mezcla de 3-butoxipirazol-5-carboxilato de metilo (5.00 g), bromuro de 4-(trifluorometil)bencilo (7.22 g), carbonato de potasio (5.22 g) y N,N-dimetilformamida (50 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua para dividir la mezcla en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:9, v/v) para dar 3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carboxilato de metilo (5.79 g, rendimiento: 64%, que contiene isómero en aproximadamente el 10%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz),

1.41 - 1.55 (2 H, m), 1.68 - 1.82 (2 H, m), 3.83 (3 H, s), 4.12 (2 H, t, J = 6.6 Hz), 5.65 (2 H, s), 6.25 (1 H, s), 7.33 (2 H, d, J = 8.1 Hz), 7.55 (2 H, d, J = 8.1 Hz).

Ejemplo de referencia 65

Una mezcla de 3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carboxilato de metilo (5.79 g), una solución acuosa 1 N de hidróxido de sodio (30 ml), tetrahidrofurano (60 ml) y etanol (60 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carboxílico (3.33 g, rendimiento: 60%) en forma de cristales incoloros. Punto de fusión 128-129°C.

Ejemplo de referencia 66

Una mezcla de clorhidrato de N,O-dimetilhidroxilamina (1.13 g), trietilamina (1.17 g) y N,N-dimetilformamida (30 ml) se agitó a temperatura ambiente durante 30 min, se añadieron ácido 3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carboxílico (3.30 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (2.22 g) y 1-hidroxibenzotriazol monohidratado (1.78 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con

acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, carbonato ácido de sodio acuoso saturado, agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v) para dar 3-butoxi-N-metoxi-N-metil-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carboxamida (3.01 g, rendimiento: 81%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.97 (3 H, t, J = 7.2 Hz), 1.41 - 1.55 (2 H, m), 1.70 - 1.81 (2 H, m), 3.27 (3 H, s), 3.55 (3 H, s), 4.15 (2 H, t, J = 6.6 Hz), 5.59 (2 H, s), 6.22 (1 H, s), 7.30 (2 H, d, J = 8.1 Hz), 7.53 (2 H, d, J = 8.1 Hz).

Ejemplo de referencia 67

A una solución de 3-butoxi-N-metoxi-N-metil-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carboxamida (3.00 g) en tetrahidrofurano (100 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (11.7 ml) a 0°C, y la mezcla se agitó durante 1 hora. Se añadió metanol para neutralizar la reacción. La mezcla de reacción se vertió en una solución acuosa al 10% de sal de Rochelle, y la mezcla se agitó y se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:17, v/v) para dar 3-butoxi-

1-[4-(trifluorometil)bencil]-1H-pirazol-5-carbaldehído (2.31 g, rendimiento: 91%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.97 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.70 - 1.82 (2 H, m), 4.16 (2 H, t, J = 6.5 Hz), 5.61 (2 H, s), 6.29 (1 H, s), 7.37 (2 H, d, J = 8.6 Hz), 7.55 (2 H, d, J = 8.6 Hz), 9.71 (1 H, s).

Ejemplo de referencia 68

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (2.38 g) en N,N-dimetilformamida (20 ml) se añadió hidruro de sodio (60% en aceite, 368 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-carbaldehído (2.31 g) en tetrahidrofurano (15 ml), y la mezcla se agitó durante 1 hora. La mezcla se calentó hasta temperatura ambiente y luego se agitó durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió para neutralizar la reacción. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:17, v/v) para dar (2E)-3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (2.02 g, rendimiento: 72%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.69 - 1.81 (2 H, m), 4.12 (2 H, t, J = 6.6 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.33 (2 H, s), 6.01 (1 H, s), 6.28 (1 H, d, J = 15.8 Hz), 7.22 (2 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 15.8 Hz), 7.57 (2 H, d, J = 8.1 Hz).

Ejemplo de referencia 69

Una mezcla de (2E)-3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (1.00 g), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (760 mg, rendimiento: 82%) en forma de cristales incoloros. Punto de fusión 153-155°C.

Ejemplo de referencia 70

Una mezcla de (2E)-3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (1.01 g), paladio-carbón al 5% (250 mg) y tetrahidrofurano (20 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró

para dar 3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoato de etilo (950 mg, rendimiento: 94%) en forma de un aceite incoloro.

Una mezcla de 3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoato de etilo (950 mg), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoico (720 mg, rendimiento: 66%) en forma de cristales incoloros. Punto de fusión 116-118°C.

Ejemplo de referencia 71

Una mezcla de 3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]propanoato de etilo (2.00 g), bromoacetato de ter-butilo (1.37 g), carbonato de potasio (1.21 g) y N,N-dimetilformamida (30 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, y el concentrado se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-

hexano (1:19 - 3:7, v/v) para dar 3-[3-(2-ter-butoxi-2-oxoetoxi)-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoato de etilo (2.03 g, rendimiento: 76%) en forma de un sólido incoloro.

Una mezcla de 3-[3-(2-ter-butoxi-2-oxoetoxi)-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoato de etilo y ácido trifluoroacético (20 ml) se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido {[1-(2,4-diclorobencil)-5-(3-etoxi-3-oxopropil)-1H-pirazol-3-il]oxi}acético (1.65 g, rendimiento: 93%) en forma de cristales incoloros. Punto de fusión 129-131°C.

Ejemplo de referencia 72

A una solución de ácido {[1-(2,4-diclorobencil)-5-(3-etoxi-3-oxopropil)-1H-pirazol-3-il]oxi}acético (400 mg) en tetrahidrofurano (7.0 ml) se añadió N,N'-carbonildiimidazol (178 mg), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió acetilhidracina (296 mg), y la mezcla se siguió agitando a temperatura ambiente durante 3 h. La mezcla de reacción se concentró, y el residuo se dividió en acetato de etilo y agua. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 3-{3-[2-(2-acetilhidrazino)-2-oxoetoxi]-1-(2,4-diclorobencil)-1H-pirazol-5-il}propanoato de etilo (410 mg, rendimiento: 90%) en forma

de cristales incoloros. Punto de fusión 167-170°C.

Ejemplo de referencia 73

Se agitaron 3-{3-[2-(2-acetilhidrazino)-2-oxoetoxi]-1-(2,4-diclorobencil)-1H-pirazol-5-il}propanoato de etilo (410 mg), pentaóxido difosfórico (510 mg), hexametildisiloxano (1.17 g) y tolueno (20 ml) con calentamiento a reflujo durante 3 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con carbonato ácido de sodio acuoso saturado y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar 3-{1-(2,4-diclorobencil)-3-[(5-metil-1,3,4-oxadiazol-2-il)metoxi]-1H-pirazol-5-il}propanoato de etilo (270 mg, rendimiento: 69%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.25 (3 H, t, J = 7.2 Hz), 2.54 (3 H, s), 2.55 - 2.62 (2 H, m), 2.74 - 2.83 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 5.20 (2 H, s), 5.33 (2 H, s), 5.62 (1 H, s), 6.56 (1 H, d, J = 8.4 Hz), 7.16 (1 H, dd, J = 2.1, 8.4 Hz), 7.39 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 74

Bajo enfriamiento con hielo, a una solución de 3-{1-(2,4-diclorobencil)-3-[(5-metil-1,3,4-oxadiazol-2-il)metoxi]-1H-pirazol-5-il}propanoato de etilo (270 mg) en tetrahidrofurano (4.0 ml) se añadió una solución de hidróxido

de litio monohidratado (28 mg) en agua (1.0 ml). La mezcla se agitó durante 20 min, se calentó hasta temperatura ambiente y luego se agitó durante 20 min. Una solución de hidróxido de litio monohidratado (28 mg) en agua (1.0 ml) se añadió a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 20 min. Una solución acuosa al 10% de ácido cítrico (50 ml) se añadió para neutralizar la reacción. La mezcla de reacción se concentró a presión reducida para evaporar el tetrahidrofurano, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar ácido 3-{1-(2,4-diclorobencil)-3-[(5-metil-1,3,4-oxadiazol-2-il)metoxi]-1H-pirazol-5-il}propanoico (250 mg) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.55 (3 H, s), 2.59 - 2.67 (2 H, m), 2.74 - 2.82 (2 H, m), 5.19 (2 H, s), 5.34 (2 H, s), 6.55 (1 H, d, J = 8.1 Hz), 7.15 (1 H, dd, J = 2.1, 8.1 Hz), 7.38 (1 H, d, J = 2.1 Hz), 11.02 (1 H, brs).

Ejemplo de referencia 75

Una mezcla de 3-butoxipirazol-5-carboxilato de metilo (7.28 g), 2-cloro-1-(clorometil)-4-(trifluorometil)benceno (38.9 g), carbonato de potasio (7.61 g) y N,N-dimetilformamida (60 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada,

se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:10, v/v) para dar 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carboxilato de metilo (9.79 g, rendimiento: 68%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.39 - 1.54 (2 H, m), 1.67 - 1.82 (2 H, m), 3.82 (3 H, s), 4.13 (2 H, t, J = 6.6 Hz), 5.76 (2 H, s), 6.32 (1 H, s), 6.66 (1 H, d, J = 8.1 Hz), 7.39 (1 H, dd, J = 1.2, 8.1 Hz), 7.64 (1 H, d, J = 1.2 Hz).

Ejemplo de referencia 76

Una mezcla de 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carboxilato de metilo (9.79 g), una solución acuosa 1 N de hidróxido de sodio (45 ml), tetrahidrofurano (90 ml) y etanol (90 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carboxílico (7.88 g, rendimiento: 83%) en forma de cristales incoloros. Punto de fusión 158-160°C.

Ejemplo de referencia 77

Una mezcla de clorhidrato de N,O-dimetilhidroxilamina (2.42 g), trietilamina (2.51 g) y N,N-dimetilformamida (100 ml) se agitó a temperatura ambiente durante 30 min, se añadieron ácido 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carboxílico (7.79 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (4.75 g) y 1-hidroxibenzotriazol monohidratado (3.80 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, carbonato ácido de sodio acuoso saturado, agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v) para dar 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-N-metoxi-N-metil-1H-pirazol-5-carboxamida (8.69 g, rendimiento: 100%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.40 - 1.55 (2 H, m), 1.70 - 1.81 (2 H, m), 3.28 (3 H, s), 3.66 (3 H, s), 4.15 (2 H, t, J = 6.6 Hz), 5.68 (2 H, s), 6.29 (1 H, s), 6.70 (1 H, d, J = 8.1 Hz), 7.38 (1 H, d, J = 8.1 Hz), 7.61 (1 H, s).

Ejemplo de referencia 78

A una solución de 3-butoxi-1-[2-cloro-4-

(trifluorometil)bencil]-N-metoxi-N-metil-1H-pirazol-5-carboxamida (8.69 g) en tetrahidrofurano (250 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (21 ml) a 0°C, y la mezcla se agitó durante 1 hora. Se añadió metanol para neutralizar la reacción. La mezcla de reacción se vertió en una solución acuosa al 10% de sal de Rochelle, y la mezcla se agitó y se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v) para dar 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carbaldehído (6.31 g, rendimiento: 84%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.40 - 1.54 (2 H, m), 1.69 - 1.81 (2 H, m), 4.16 (2 H, t, J = 6.6 Hz), 5.73 (2 H, s), 6.36 (1 H, s), 6.70 (1 H, d, J = 7.8 Hz), 7.39 (1 H, dd, J = 1.2, 7.8 Hz), 7.65 (1 H, d, J = 7.8 Hz), 9.75 (1 H, s).

Ejemplo de referencia 79

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (3.26 g) en N,N-dimetilformamida (25 ml) se añadió hidruro de sodio (60% en aceite, 504 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-

carbaldehído (3.50 g) en tetrahidrofurano (22 ml), y la mezcla se agitó durante 1 hora. La mezcla se calentó hasta temperatura ambiente y luego se agitó durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió para neutralizar la reacción. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:49 - 1:9, v/v) para dar (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (1.74 g, rendimiento: 42%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.69 - 1.81 (2 H, m), 4.12 (2 H, t, J = 6.6 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.33 (2 H, s), 6.01 (1 H, s), 6.28 (1 H, d, J = 15.8 Hz), 7.22 (2 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 15.8 Hz), 7.57 (2 H, d, J = 8.1 Hz).

Ejemplo de referencia 80

Una mezcla de (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (1.86 g), una solución acuosa 1 N de hidróxido de sodio (10 ml), tetrahidrofurano (20 ml) y etanol (20 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con

acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (730 mg, rendimiento: 42%) en forma de cristales incoloros. Punto de fusión 172-174°C.

Ejemplo de referencia 81

Una mezcla de (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (1.70 g), paladio-carbón al 5% (360 mg) y tetrahidrofurano (30 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró para dar 3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoato de etilo (1.67 g, rendimiento: 98%) en forma de un aceite de color amarillo pálido.

Una mezcla de 3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoato de etilo (1.67 g), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-

il}propanoico (1.25 g, rendimiento: 80%) en forma de cristales incoloros. Punto de fusión 125-126°C.

Ejemplo de referencia 82

Una mezcla de 3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]propanoato de etilo (2.00 g), 2-(clorometil)piridina (573 mg), carbonato de potasio (1.01 g) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v) para dar 3-[1-(2,4-diclorobencil)-3-(piridin-2-ilmetoxi)-1H-pirazol-5-il]propanoato de etilo (1.00 g, rendimiento: 79%) en forma de un sólido incoloro.

Una mezcla de 3-[1-(2,4-diclorobencil)-3-(piridin-2-ilmetoxi)-1H-pirazol-5-il]propanoato de etilo (1.00 g), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió agua (200 ml), y los cristales precipitados se recogieron por filtración para dar ácido 3-[1-(2,4-diclorobencil)-3-(piridin-2-ilmetoxi)-1H-pirazol-5-il]propanoico (0.76 g, rendimiento: 75%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.46 - 2.56 (2 H, m), 2.67 -

2.77 (2 H, m), 5.15 (2 H, s), 5.20 (2 H, s), 5.72 (1 H, s), 6.62 (1 H, d, J = 8.4 Hz), 7.27 - 7.34 (1 H, m), 7.35 (1 H, dd, J = 2.1, 8.4 Hz), 7.43 (1 H, d, J = 7.8 Hz), 7.65 (1 H, d, J = 2.1 Hz), 7.77 - 7.84 (1 H, m), 8.51 - 8.56 (1 H, m), 12.30 (1 H, brs).

Ejemplo de referencia 83

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-hidroxi-1H-pirazol-5-il}acrilato de etilo (275 mg), bromometilciclopropano (560 mg), carbonato de potasio (760 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, y el concentrado se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrilato de etilo (690 mg, rendimiento: 59%) en forma de cristales incoloros.

Una mezcla de (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrilato de etilo (400 mg), una solución acuosa 1 N de hidróxido de sodio (3.0 ml), tetrahidrofurano (6.0 ml) y etanol (6.0 ml) se agitó a 50°C durante 1 hora. La mezcla de

reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrílico (300 mg, rendimiento: 80%) en forma de cristales incoloros. Punto de fusión 195-196°C.

Ejemplo de referencia 84

Se agitaron (2E)-3-[1-(2,4-Diclorobencil)-3-(metoximetoxi)-1H-pirazol-5-il]acrilato de etilo (2.49 g), ácido clorhídrico concentrado (0.15 ml) y metanol (30 ml) con calentamiento a reflujo durante 5 h. La mezcla de reacción se concentró, y el residuo se cristalizó en éter diisopropílico-hexano-acetato de etilo para dar (2E)-3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]acrilato de etilo (2.41 g) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.31 (3 H, t, J = 7.2 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.28 (2 H, s), 5.95 (1 H, s), 6.32 (1 H, d, J = 15.6 Hz), 6.72 (1 H, d, J = 8.4 Hz), 7.17 (1 H, dd, J = 2.1, 8.4 Hz), 7.38 (1 H, d, J = 15.6 Hz), 7.41 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 85

A una solución de (2E)-3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]acrilato de etilo (1.20 g), 2-

metoxietanol (533 mg) y tributilfosfina (1.42 g) en tetrahidrofurano (70 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.77 g), y la mezcla se agitó a temperatura ambiente durante 15 horas y se concentró. Se añadió éter diisopropílico al residuo, el material insoluble restante se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:1, v/v) para dar (2E)-3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]acrilato de etilo (850 mg, rendimiento: 61%) en forma de cristales incoloros.

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]acrilato de etilo (850 mg), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]acrílico (300 mg, rendimiento: 91%) en forma de cristales incoloros. Punto de fusión 171-172°C.

Ejemplo de referencia 86

Una mezcla de 3-hidroxi-1H-pirazol-5-carboxilato de

metilo (68.6 g), éster clorometilmetílico (46.7 g), carbonato de potasio (100 g) y N,N-dimetilformamida (350 ml) se agitó a temperatura ambiente durante 15 h, se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa acuosa se extrajo con cloroformo, los extractos se combinaron, y la mezcla se concentró. El residuo se disolvió en cloroformo, y la solución se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:12 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-(metoximetoxi)-1H-pirazol-5-carboxilato de metilo (23.4 g, rendimiento: 26%) en forma de cristales incoloros. Punto de fusión 54-55°C.

Ejemplo de referencia 87

Una mezcla de 3-(metoximetoxi)-1H-pirazol-5-carboxilato de metilo (23.4 g), cloruro de 2-cloro-4-trifluorometilbencilo (30.0 g), carbonato de potasio (26.1 g) y N,N-dimetilformamida (120 ml) se agitó a temperatura ambiente durante 15 h, se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:10, v/v) para dar 1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-carboxilato de metilo (34.1 g, rendimiento: 71%) en

forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.53 (3 H, s), 3.83 (3 H, s), 5.24 (2 H, s), 5.79 (2 H, s), 6.46 (1 H, s), 6.70 (1 H, d, J = 8.1 Hz), 7.43 (1 H, dd, J = 0.9, 8.1 Hz), 7.65 (1 H, d, J = 0.9 Hz).

Ejemplo de referencia 88

Una mezcla de 1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-carboxilato de metilo (34.1 g), una solución acuosa 1 N de hidróxido de sodio (150 ml), tetrahidrofurano (250 ml) y etanol (250 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-carboxílico (28.1 g, rendimiento: 86%) en forma de cristales incoloros. Punto de fusión 133-134°C.

Ejemplo de referencia 89

Una mezcla de clorhidrato de N,O-dimetilhidroxilamina (9.01 g), trietilamina (9.35 g) y N,N-dimetilformamida (300 ml) se agitó a temperatura ambiente durante 30 min, se añadieron ácido 1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-carboxílico (28.1 g), clorhidrato de 1-etil-3-(3-

dimetilaminopropil)carbodiimida (17.7 g) y 1-hidroxibenzotriazol monohidratado (14.2 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con ácido clorhídrico 1 N, solución acuosa saturada de carbonato ácido de sodio, agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar 1-[2-cloro-4-(trifluorometil)bencil]-N-metoxi-3-(metoximetoxi)-N-metil-1H-pirazol-5-carboxamida (29.1 g, rendimiento: 93%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.29 (3 H, s), 3.53 (3 H, s), 3.67 (3 H, s), 5.25 (2 H, s), 5.70 (2 H, s), 6.41 (1 H, s), 6.75 (1 H, d, J = 8.1 Hz), 7.40 (1 H, d, J = 8.1 Hz), 7.62 (1 H, s).

Ejemplo de referencia 90

A una solución de 1-[2-cloro-4-(trifluorometil)bencil]-N-metoxi-3-(metoximetoxi)-N-metil-1H-pirazol-5-carboxamida (29.1 g) en tetrahidrofurano (500 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (71.0 ml) a 0°C, y la mezcla se agitó durante 1 hora. Se añadió metanol para neutralizar la reacción. La mezcla de reacción se vertió en una solución acuosa al 10% de sal de Rochelle, y la mezcla se agitó y se

extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v) para dar 1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-carbaldehído (21.2 g, rendimiento: 85%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.53 (3 H, s), 5.75 (2 H, s), 6.51 (1 H, s), 6.75 (1 H, d, J = 8.1 Hz), 7.40 (1 H, d, J = 8.1 Hz), 7.65 (1 H, s), 9.76 (1 H, s).

Ejemplo de referencia 91

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (16.6 g) en N,N-dimetilformamida (100 ml) se añadió hidruro de sodio (60% en aceite, 2.56 g), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-carbaldehído (17.2 g) en tetrahidrofurano (110 ml), y la mezcla se agitó durante 1 hora. La mezcla se calentó hasta temperatura ambiente y luego se agitó durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió para neutralizar la reacción. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía

en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:3, v/v) para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-il}acrilato de etilo (12.4 g, rendimiento: 60%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.30 (3 H, t, J = 7.2 Hz), 3.53 (3 H, s), 4.23 (2 H, t, J = 7.2 Hz), 5.23 (2 H, s), 5.43 (2 H, s), 6.18 (1 H, s), 6.32 (1 H, d, J = 15.5 Hz), 6.83 (1 H, d, J = 8.1 Hz), 7.39 (1 H, d, J = 15.5 Hz), 7.43 (1 H, d, J = 8.1 Hz), 7.66 (1 H, s).

Ejemplo de referencia 92

Se agitaron (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-(metoximetoxi)-1H-pirazol-5-il}acrilato de etilo (8.40 g), ácido clorhídrico concentrado (0.30 ml) y metanol (70 ml) con calentamiento a reflujo durante 5 h. La mezcla de reacción se concentró, y el residuo se cristalizó en éter diisopropílico-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-hidroxi-1H-pirazol-5-il}acrilato de etilo (6.53 g) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.30 (3 H, t, J = 7.2 Hz), 4.23 (2 H, q, J = 7.2 Hz), 5.36 (2 H, s), 5.98 (1 H, s), 6.34 (1 H, d, J = 15.8 Hz), 6.84 (1 H, d, J = 8.1 Hz), 7.36 (1 H, d, 8.1 Hz), 7.67 (1 H, s).

Ejemplo de referencia 93

Se agitaron (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-hidroxi-1H-pirazol-5-il}acrilato de etilo (1.20 g), 2-yodopropano (653 mg), carbonato de potasio

(663 mg) y N,N-dimetilformamida (20 ml) a temperatura ambiente durante 15 h, la mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 7:3, v/v) para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}etil acrilato de etilo (1.08 g, 81%) en forma de cristales blancos.

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}etilacrilato de etilo (1.38 g), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}acrílico (1.22 g, rendimiento: 95%) en forma de cristales incoloros. Punto de fusión 170-171°C.

Ejemplo de referencia 94

A una solución de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-hidroxi-1H-pirazol-5-il}acrilato de etilo (500 mg), (3-metiloxetan-3-il)metanol (160 mg) y

tributilfosfina (540 mg) en tetrahidrofurano (15 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (620 mg), y la mezcla se agitó a temperatura ambiente durante 2 horas y se concentró. Se añadió éter diisopropílico al residuo, el material insoluble restante se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (3:17 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-[(3-metiloxetan-3-il)metoxi]-1H-pirazol-5-il}acrilato de etilo (560 mg, rendimiento: 91%) en forma de un aceite incoloro.

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-[(3-metiloxetan-3-il)metoxi]-1H-pirazol-5-il}acrilato de etilo (560 mg), una solución acuosa 1 N de hidróxido de sodio (2.4 ml), tetrahidrofurano (7 ml) y etanol (7 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (20 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-[(3-metiloxetan-3-il)metoxi]-1H-pirazol-5-il}acrílico (425 mg, rendimiento: 82%) en forma de cristales incoloros. Punto de fusión 148-149°C.

Ejemplo de referencia 95

A una solución (calentada hasta 60°C) de (2E)-3-[1-(2,4-diclorobencil)-3-hidroxi-1H-pirazol-5-il]acrilato de etilo (1.50 g), tetrahidro-2H-piran-4-ol (893 mg) y tributilfosfina (1.77 g) en tetrahidrofurano (60 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.77 g), y la mezcla se agitó durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró. Se añadió éter diisopropílico al residuo, el material insoluble restante se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 1:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrilato de etilo (1.47 g, rendimiento: 79%) en forma de cristales incoloros.

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrilato de etilo (1.50 g), una solución acuosa 1 N de hidróxido de sodio (8.0 ml), tetrahidrofurano (15 ml) y etanol (15 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-

3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrílico (1.35 g, rendimiento: 96%) en forma de cristales incoloros. Punto de fusión 191-192°C.

Ejemplo de referencia 96

A una solución (calentada hasta 60°C) de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-hidroxi-1H-pirazol-5-il}acrilato de etilo (1.26 g), tetrahidro-2H-piran-4-ol (687 mg) y tributilfosfina (1.36 g) en tetrahidrofurano (50 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.70 g), y la mezcla se agitó durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró. Se añadió éter diisopropílico al residuo, el material insoluble restante se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 1:3, v/v) para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrilato de etilo (1.16 g, rendimiento: 75%) en forma de cristales incoloros.

Una mezcla de (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrilato de etilo (1.16 g), una solución acuosa 1 N de hidróxido de sodio (5.0 ml), tetrahidrofurano (10 ml) y etanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de

acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrílico (1.07 g, rendimiento: 98%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.73 - 1.87 (2 H, m), 2.00 - 2.13 (2 H, m), 3.48 - 3.63 (2 H, m), 3.92 - 4.04 (2 H, m), 4.64 - 4.76 (1 H, m), 5.41 (2 H, s), 6.09 (1 H, s), 6.29 (1 H, d, J = 15.6 Hz), 6.77 (1 H, d, J = 8.1Hz), 7.44 (1 H, d, J = 8.1Hz), 7.45 (1 H, d, J = 15.6 Hz), 7.67 (1 H, s).

Ejemplo de referencia 97

A una mezcla de ter-butóxido de potasio (94.1 g) y tetrahidrofurano (500 ml) se añadió gota a gota una mezcla de acetilciclopropano (50.0 g) y oxalato de dietilo (87.8 g), y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron ácido acético (81.3 ml) y monohidrato de hidracina (32.7 g) a la mezcla de reacción, y la mezcla se agitó con calentamiento a reflujo durante 2 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con solución acuosa saturada de carbonado de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en éter diisopropílico para dar 3-ciclopropil-1H-pirazol-5-carboxilato de etilo (64.5 g, rendimiento: 60%) en forma de cristales marrones.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.68 - 0.82 (2 H, m), 0.90 - 1.06 (2 H, m), 1.34 (3 H, t, J = 7.2 Hz), 1.88 - 2.04 (1 H, m), 4.36 (2 H, q, J = 7.2 Hz), 6.45 (1 H, s), 11.30 (1 H, brs).

Ejemplo de referencia 98

Una mezcla de 3-ciclopropil-1H-pirazol-5-carboxilato de etilo (20.0 g), cloruro de 2-cloro-4-trifluorometilbencilo (28.0 g), carbonato de potasio (23.0 g) y N,N-dimetilformamida (200 ml) se agitó a temperatura ambiente durante 15 h, se concentró y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v) para dar 1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-carboxilato de etilo (23.2 g, rendimiento: 56%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.72 - 0.80 (2 H, m), 0.92 - 1.02 (2 H, m), 1.29 (3 H, t, J = 7.2 Hz), 1.90 - 2.02 (1H, m), 4.25 (2 H, q, J = 7.2 Hz), 5.82 (2 H, s), 6.53 (1 H, d, J = 8.1Hz), 6.62 (1 H, s), 7.38 (1 H, d, J = 8.1Hz), 7.64 (1 H, s).

Ejemplo de referencia 99

A una solución de 1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-carboxilato

de etilo (23.2 g) en tetrahidrofurano (300 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (104 ml) a 0°C. La mezcla se agitó a temperatura ambiente durante 1 hora, y Se añadió sulfato de sodio decahidratado para neutralizar la reacción. El material insoluble se filtró, y el filtrado se concentró. El residuo se disolvió en acetato de etilo, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar {1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}metanol (17.2 g, rendimiento: 84%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.68 - 0.75 (2 H, m), 0.88 - 0.98 (2 H, m), 1.63 (1 H, t, J = 5.7 Hz), 1.88 - 1.99 (1 H, m), 4.55 (2 H, d, J = 5.7 Hz), 5.45 (2 H, s), 5.96 (1 H, s), 6.66 (1 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 8.1 Hz), 7.63 (1 H, s).

Ejemplo de referencia 100

Bajo una atmósfera de nitrógeno, a una solución de cloruro de oxalilo (13.1 g) en diclorometano (150 ml) se añadió dimetilsulfóxido (12.1 g) a -78°C, y la mezcla se agitó durante 5 min. Se añadió una solución de {1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}metanol (17.1 g) en diclorometano (200 ml). Tras agitar a -78°C durante 1 hora, se agregó trietilamina (26.2 g), y la mezcla de reacción se calentó hasta temperatura ambiente y luego se agitó durante 1 h. La mezcla de reacción se concentró, y el

residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-carbaldehído (14.3 g, rendimiento: 84%) en forma de cristales de color amarillo pálido. Punto de fusión 94-96°C.

Ejemplo de referencia 101

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (14.6 g) en N,N-dimetilformamida (100 ml) se añadió hidruro de sodio (60% en aceite, 2.26 g), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-carbaldehído (14.3 g) en tetrahidrofurano (100 ml), y la mezcla se agitó durante 1 hora. La mezcla de reacción se calentó hasta temperatura ambiente y luego se agitó durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió para neutralizar la reacción. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:3, v/v) para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-

il}acrilato de etilo (16.9 g, rendimiento: 97%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.72 - 0.80 (2 H, m), 0.92 - 1.01 (2 H, m), 1.30 (3 H, t, J = 7.2 Hz), 1.88 - 2.00 (1 H, m), 4.22 (2 H, q, J = 7.2 Hz), 5.49 (2 H, s), 6.29 (1 H, d, J = 15.8 Hz), 6.66 (1 H, d, J = 8.1 Hz), 7.38 (1 H, d, J = 15.8 Hz), 7.42 (1 H, d, J = 8.1 Hz), 7.66 (1 H, s).

Ejemplo de referencia 102

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}acrilato de etilo (8.90 g), paladio-carbón al 5% (1.91 g) y tetrahidrofurano (15 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo se disolvió en tetrahidrofurano (80 ml), se añadieron etanol (80 ml) y solución acuosa 1 N de hidróxido de sodio (40 ml), y la mezcla se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}propanoico (1.80 g, rendimiento: 86%, con ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-propil-1H-pirazol-5-

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il}propanoico en un 9%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.66 - 0.74 (2 H, m), 0.87 - 0.97 (2 H, m), 1.85 - 1.98 (1 H, m), 2.60 - 2.67 (2 H, m), 2.72 - 2.79 (2 H, m), 5.36 (2 H, s), 5.80 (1 H, s), 6.59 (1 H, d, J = 8.1 Hz), 7.40 (1 H, dd, J = 0.9, 8.1 Hz), 7.66 (1 H, d, J = 0.9 Hz).

Ejemplo de referencia 103

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}acrilato de etilo (8.00 g), una solución acuosa 1 N de hidróxido de sodio (40 ml), tetrahidrofurano (80 ml) y etanol (80 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar ácido (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}acrílico (6.40 g, rendimiento: 86%) en forma de un sólido blanco. Punto de fusión 191-192°C.

Ejemplo de referencia 104

Una mezcla de (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrilato de etilo (690 mg), paladio-carbón al 5% (130 mg) y tetrahidrofurano (15 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el

filtrado se concentró para dar 3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]propanoato de etilo (650 mg, rendimiento: 94%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.28 - 0.37 (2 H, m), 0.54 - 0.64 (2 H, m), 1.18 - 1.32 (4 H, m), 2.53 - 2.64 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 5.26 (2 H, s), 5.59 (1 H, s), 6.68 (1 H, d, J = 8.1 Hz), 7.42 (1 H, d, J = 8.1 Hz), 7.64 (1 H, s).

Ejemplo de referencia 105

Una mezcla de 3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]propanoato de etilo (650 mg), una solución acuosa 1 N de hidróxido de sodio (4.0 ml), tetrahidrofurano (8.0 ml) y etanol (8.0 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (50 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]propanoico (510 mg, rendimiento: 84%) en forma de cristales incoloros. Punto de fusión 115-116°C.

Ejemplo de referencia 106

A una mezcla de ter-butóxido de potasio (64.8 g) y

tetrahidrofurano (500 ml) se añadió gota a gota una mezcla de 3.3-dimetil-2-butanona (41.0 g) y oxalato de dietilo (60.4 g), y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron ácido acético (56.0 ml) y monohidrato de hidracina (22.5 g) a la mezcla de reacción, y la mezcla se agitó con calentamiento a reflujo durante 2 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, y el residuo se vertió en agua. El precipitado resultante se recogió por filtración para dar 3-ter-butil-1H-pirazol-5-carboxilato de etilo (65.6 g, rendimiento: 82%) en forma de un sólido anaranjado.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.278 (9 H, s), 1.282 (3 H, t, J = 7.2 Hz), 4.25 (2 H, q, J = 7.2 Hz), 6.49 (1 H, brs), 13.22 (1 H, brs).

Ejemplo de referencia 107

Una mezcla de 3-ter-butil-1H-pirazol-5-carboxilato de etilo (20.0 g), cloruro de 2-cloro-4-trifluorometilbencilo (24.1 g), carbonato de potasio (21.1 g) y N,N-dimetilformamida (200 ml) se agitó a temperatura ambiente durante 15 h, y la mezcla de reacción se concentró. El residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:6, v/v) para dar 3-ter-butil-1-[2-cloro-4-

(trifluorometil)bencil]-1H-pirazol-5-carboxilato de etilo (36.8 g, rendimiento: 93%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.2 Hz), 1.34 (9 H, s), 4.25 (2 H, q, J = 7.2 Hz), 5.85 (2 H, s), 6.43 (1 H, d, J = 8.1Hz), 6.83 (1 H, s), 7.37 (1 H, d, J = 8.1Hz), 7.64 (1 H, s).

Ejemplo de referencia 108

A una solución de 3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carboxilato de etilo (23.2 g) en tetrahidrofurano (400 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (158 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió sulfato de sodio decahidratado para neutralizar la reacción. El material insoluble se filtró, y el filtrado se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar {3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}metanol (7.69 g, rendimiento: 23%) en forma de cristales incoloros. Punto de fusión 115-117°C.

Ejemplo de referencia 109

Bajo una atmósfera de nitrógeno, a una solución de cloruro de oxalilo (7.47 g) en diclorometano (50 ml) se añadió dimetilsulfóxido (6.89 g) a -78°C, y la mezcla se agitó durante 5 min. Se agregó una solución de {3-ter-butil-1-[2-cloro-4-

(trifluorometil)bencil]-1H-pirazol-5-il}metanol (10.2 g) en diclorometano (80 ml). Tras agitar a -78°C durante 1 hora, se añadió trietilamina (14.9 g), y la mezcla de reacción se calentó hasta temperatura ambiente y luego se agitó durante 1 h. La mezcla de reacción se concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carbaldehído (8.16 g, rendimiento: 81%) en forma de cristales de color amarillo pálido. Punto de fusión 147-149°C.

Ejemplo de referencia 110

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (7.50 g) en N,N-dimetilformamida (50 ml) se añadió hidruro de sodio (60% en aceite, 1.16 g), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-carbaldehído (8.16 g) en tetrahidrofurano (50 ml), y la mezcla se agitó durante 1 hora. La mezcla de reacción se calentó hasta temperatura ambiente y luego se agitó durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió para neutralizar la reacción. La mezcla de reacción se concentró, y

el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v) para dar (2E)-3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (9.82 g, rendimiento: 100%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.2 Hz), 1.33 (9 H, s), 4.21 (2 H, q, J = 7.2 Hz), 5.53 (2 H, s), 6.32 (1 H, d, J = 15.8 Hz), 6.56 (1 H, d, J = 8.4 Hz), 7.37 (1 H, d, J = 15.8 Hz), 7.41 (1 H, d, J = 8.4 Hz), 7.66 (1 H, s).

Ejemplo de referencia 111

Una mezcla de (2E)-3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (3.00 g), una solución acuosa 1 N de hidróxido de sodio (20 ml), tetrahidrofurano (40 ml) y etanol (40 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (2.24 g, rendimiento: 80%) en forma de cristales incoloros. Punto de fusión 175-176°C.

Ejemplo de referencia 112

Una mezcla de (2E)-3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrilato de etilo (3.00 g), paladio-carbón al 5% (500 mg) y tetrahidrofurano (50 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró para dar 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoato de etilo (2.53 g, rendimiento: 84%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.2 Hz), 1.31 (9 H, s), 2.55 - 2.65 (2 H, m), 2.72 - 2.82 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 5.39 (2 H, s), 6.00 (1 H, s), 6.47 (1 H, d, J = 8.1 Hz), 7.41 (1 H, d, J = 8.1 Hz), 7.63 (1 H, s).

Ejemplo de referencia 113

Una mezcla de 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoato de etilo (2.53 g), una solución acuosa 1 N de hidróxido de sodio (15 ml), tetrahidrofurano (30 ml) y etanol (30 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (200 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-

il}propanoico (2.08 g, rendimiento: 88%) en forma de cristales incoloros. Punto de fusión 128-129°C.

Ejemplo de referencia 114

Una mezcla de ({(E)-2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]vinil}sulfonil)carbamato de terbutilo (1.03 g) y ácido trifluoroacético (20 ml) se agitó a temperatura ambiente durante 1 hora y la mezcla de reacción se concentró. Una solución acuosa saturada de carbonato ácido de sodio se añadió al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar (E)-2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etilensulfonamida (710 mg, rendimiento: 87%) en forma de cristales incoloros. Punto de fusión 158-160°C.

Ejemplo de referencia 115

Una mezcla de (E)-2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etilensulfonamida (350 mg), paladio sobre carbón al 5% (140 mg) y tetrahidrofurano (15 ml) se hidrogenó a temperatura ambiente a presión atmosférica durante 15 h. La mezcla de reacción se filtró, y el filtrado se concentró. Una mezcla del residuo, paladio-carbón al 5% (200 mg) y tetrahidrofurano (15 ml) se hidrogenó nuevamente a temperatura ambiente a presión atmosférica durante 15 h. La mezcla de reacción se filtró, y el filtrado se concentró. El

residuo se cristalizó en acetato de etilo-hexano para dar 2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etansulfonamida (260 mg, rendimiento: 74%) en forma de cristales incoloros. Punto de fusión 142-143°C.

Ejemplo de referencia 116

Una mezcla de ({(E)-2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]vinil}sulfonil)carbamato de ter-butilo (1.55 g) y ácido trifluoroacético (15 ml) se agitó a temperatura ambiente durante 1 hora, y la mezcla de reacción se concentró. Una solución acuosa saturada de carbonato ácido de sodio se añadió al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar (E)-2-[1-(2,4-diclorobencil)-3-butoxi-1H-pirazol-5-il]etilensulfonamida (1.10 g, rendimiento: 89%) en forma de cristales incoloros. Punto de fusión 105-108°C.

Ejemplo de referencia 117

Una mezcla de (E)-2-[1-(2,4-diclorobencil)-3-butoxi-1H-pirazol-5-il]etilensulfonamida (1.35 g), paladio-carbón al 5% (920 mg) y tetrahidrofurano (50 ml) se hidrogenó a temperatura ambiente a presión atmosférica durante 24 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-

il]etansulfonamida (1.10 g, rendimiento: 81%) en forma de cristales incoloros. Punto de fusión 134-136°C.

Ejemplo de referencia 118

A una solución de 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}propionato de etilo (5.70 g) en tetrahidrofurano (15 ml) y etanol (15 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (29.0 ml), y la mezcla se agitó a 50°C durante 30 min. Se añadió ácido clorhídrico 1 N (29.0 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}propiónico (4.09 g, rendimiento: 77%) en forma de agujas finas blancas. Punto de fusión 121.5-122.0°C.

Ejemplo de referencia 119

A una solución de 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carboxilato de metilo (41.63 g) en tetrahidrofurano (200 ml) se añadió solución toluénica 1.5 M de hidruro de diisobutilaluminio (300 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 10 min. Una solución acuosa saturada de cloruro de amonio (85.0 ml) se añadió a la mezcla de reacción, y el sólido precipitado se filtró y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en

columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:2, v/v) para dar [3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]metanol (24.51 g, rendimiento: 64%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.95 (3 H, t, J = 7.3 Hz), 1.20 - 1.53 (2 H, m), 1.66 - 1.89 (2 H, m), 4.05 - 4.21 (2 H, m), 4.47 - 4.63 (2 H, m), 5.28 (2 H, d, J = 1.5 Hz), 5.72 (1 H, d, J = 2.1 Hz), 6.59 - 6.68 (1 H, m), 7.14 (1 H, d, J = 8.5 Hz), 7.34 - 7.41 (1 H, m).

Ejemplo de referencia 120

A una solución de [3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]metanol (1.71 g) en tetrahidrofurano (40 ml) se añadieron tributilfosfina (2.40 ml), acetona de cianhidrina (0.70 ml) y 1.1'-azodicarbonildipiperidina (2.40 g), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:3, v/v) para dar un aceite amarillo.

A una solución del aceite obtenido en etanol (25 ml) se añadió solución acuosa 4 N de hidróxido de sodio (13.0 ml), y la mezcla se agitó con calentamiento a reflujo durante 1.5 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 6 N (9.0 ml) a la mezcla de reacción, y la mezcla

se diluyó con tolueno, se concentró y se disolvió en acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido [3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acético (890 mg, rendimiento: 48%) en forma de cristales blancos. Punto de fusión 105-108°C.

Ejemplo de referencia 121

A una solución de [3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrilato de etilo (6.31 g) en tetrahidrofurano (100 ml) se añadió paladio-carbón al 5% (4.30 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró y el filtrado se concentró para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en tetrahidrofurano (100 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (40 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 10 min. Una solución acuosa saturada de cloruro de amonio (12.0 ml) se añadió a la mezcla de reacción, y el sólido precipitado se filtró y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en tetrahidrofurano (100 ml) se añadieron tributilfosfina (5.90 ml), acetona de cianhidrina (2.0 ml) y 1.1'-azodicarbonildipiperidina (5.31 g), y la mezcla se agitó a temperatura ambiente durante 1 hora, y a 50°C durante 30 min. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:4, v/v) para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en etanol (30 ml) se añadió solución acuosa 4 N de hidróxido de sodio (5.0 ml), y la mezcla se agitó con calentamiento a reflujo durante 1 hora y 20 min. Luego se añadió una solución acuosa 4 N de hidróxido de sodio (2.5 ml), y la mezcla se agitó durante la noche con calentamiento a reflujo. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 6 N (5.0 ml) se añadió a la mezcla de reacción, y la mezcla se diluyó con tolueno, se concentró y se disolvió en acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar ácido 4-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]butanoico (2.86 g, rendimiento: 47%) en forma de un aceite anaranjado. Una parte se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 3:2, v/v) para dar un sólido

blanco. La recristalización en acetato de etilo-hexano dio agujas finas blancas. Punto de fusión 60.5-61.0°C.

Ejemplo de referencia 122

Se añadió ácido 4-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]butanoico (630 mg) a una solución en tetrahidrofurano 1.0 M de complejo de borano-tetrahidrofurano (6.0 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar un aceite incoloro.

A una solución del aceite obtenido en tetrahidrofurano (20 ml) se añadieron tributilfosfina (0.80 ml), acetona de cianhidrina (0.25 ml) y 1.1'-azodicarbonildipiperidina (0.80 g), y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar un aceite incoloro.

A una solución del aceite obtenido en etanol (5 ml)

se añadió una solución acuosa 4 N de hidróxido de sodio (4.0 ml), y la mezcla se agitó con calentamiento a reflujo durante 3 h. Luego se añadió una solución acuosa 8 N de hidróxido de sodio (3.0 ml), y la mezcla se siguió agitando con calentamiento a reflujo durante 4 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con tolueno, se concentró y se disolvió en acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar ácido 5-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]pentanoico (433 mg, rendimiento: 63%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.95 (3 H, t, J = 7.4 Hz), 1.35 - 1.85 (8 H, m), 2.32 (2 H, t, J = 6.9 Hz), 2.44 (2 H, t, J = 7.1 Hz), 4.10 (2 H, q, J = 6.7 Hz), 5.15 (2 H, s), 5.55 (1 H, s), 6.56 (1 H, d, J = 8.5 Hz), 7.14 (1 H, dd, J = 8.5, 2.1 Hz), 7.37 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 123

A una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-hidroxi-1H-pirazol-5-il}acrilato de etilo (1.49 g), 2-metoxietanol (0.347 ml), tributilfosfina (2.49 ml) y tetrahidrofurano (30 ml) se añadió 1.1'-azodicarbonildipiperidina (2.02 g) a 50°C, y la mezcla se agitó durante 1 hora. La solución de reacción se concentró, se añadió éter diisopropílico al residuo, y el material insoluble

se filtró. El agua madre se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:100 - 1:4, v/v) para dar un aceite incoloro (1.31 g).

Una mezcla del aceite obtenido, una solución acuosa 1 N de hidróxido de sodio (20 ml), tetrahidrofurano (20 ml) y etanol (20 ml) se agitó a temperatura ambiente durante 8 h, se añadió ácido clorhídrico 1 N (20 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. Los cristales crudos obtenidos se recristalizaron en tetrahidrofurano-hexano para dar ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(2-metoxietoxi)-1H-pirazol-5-il]acrílico (1.14 g, rendimiento: 70%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.44 (3 H, s), 3.66 - 3.81 (2 H, m), 4.22 - 4.40 (2 H, m), 5.41 (2 H, s), 6.13 (1 H, s), 6.29 (1 H, d, J = 15.8 Hz), 6.77 (1 H, d, J = 8.1 Hz), 7.36 - 7.52 (2 H, m), 7.66 (1 H, d, J = 0.9 Hz).

Ejemplo de referencia 124

Bajo enfriamiento con hielo, se añadió a una mezcla de 3-butoxipirazol-5-carboxilato de metilo (43.1 g), carbonato de potasio (36.0 g) y N,N-dimetilformamida (300 ml) cloruro de 2,4-diclorobencilo (33.2 ml), y la mezcla se agitó a temperatura ambiente durante 12 h. La mezcla de reacción se

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concentró, y el residuo se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:15, v/v) para dar 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carboxilato de metilo (56.0 g, rendimiento: 72%, que contiene isómero en aproximadamente el 10%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.40 - 1.53 (2 H, m), 1.69 - 1.79 (2 H, m), 3.81 (3 H, s), 4.12 (2 H, t, J = 6.6 Hz), 5.67 (2 H, s), 6.29 (1 H, s), 6.53 (1 H, d, J = 8.7 Hz), 7.11 (1 H, dd, J = 2.1, 8.1 Hz), 7.38 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 125

A una mezcla de 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carboxilato de metilo (55.6 g), tetrahidrofurano (200 ml) y metanol (100 ml) se añadió una solución de hidróxido de sodio (12.5 g) en agua (100 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (320 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carboxílico (33.6 g, rendimiento: 62%) en forma de

cristales incoloros. Punto de fusión 154-155°C.

Ejemplo de referencia 126

Una mezcla de clorhidrato de N,O-dimetilhidroxilamina (11.4 g), trietilamina (11.9 g) y N,N-dimetilformamida (300 ml) se agitó a temperatura ambiente durante 30 min, se agregaron ácido 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carboxílico (33.6 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (22.5 g) y 1-hidroxibenzotriazol monohidratado (18.0 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, el residuo se disolvió en acetato de etilo, y la mezcla se lavó con agua, ácido clorhídrico 1 N, una solución acuosa de carbonato de potasio y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:8 - 1:2, v/v) para dar 3-butoxi-1-(2,4-diclorobencil)-N-metoxi-N-metil-1H-pirazol-5-carboxamida (37.4 g, rendimiento: 99%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.2 Hz), 1.40 - 1.53 (2 H, m), 1.69 - 1.79 (2 H, m), 3.28 (3 H, s), 3.63 (3 H, s), 4.14 (2 H, t, J = 6.6 Hz), 5.59 (2 H, s), 6.24 (1 H, s), 6.60 (1 H, d, J = 8.1 Hz), 7.11 (1 H, dd, J = 2.1, 8.4 Hz), 7.35 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 127

A una solución de 3-butoxi-1-(2,4-diclorobencil)-N-metoxi-N-metil-1H-pirazol-5-carboxamida (37.4 g) en

tetrahidrofurano (500 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (97 ml) a 0°C, y la mezcla se agitó durante 1 hora. Se agregó sulfato de sodio decahidratado (50.0 g) para neutralizar la reacción. La mezcla de reacción se agitó a temperatura ambiente durante 5 h, el material insoluble se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:10, v/v) para dar 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carbaldehído (29.9 g, rendimiento: 94%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.97 (3 H, t, J = 7.2 Hz), 1.40 - 1.53 (2 H, m), 1.70 - 1.80 (2 H, m), 4.15 (2 H, t, J = 6.6 Hz), 5.64 (2 H, s), 6.33 (1 H, s), 6.59 (1 H, d, J = 8.1 Hz), 7.12 (1 H, d, J = 2.1, 8.1 Hz), 7.39 (1 H, d, J = 8.1 Hz), 9.74 (1 H, s).

Ejemplo de referencia 128

Bajo enfriamiento con hielo, se añadió a una solución de dietilfosfonoacetato de etilo (10.3 g) en N,N-dimetilformamida (50 ml) hidruro de sodio (60% en aceite, 1.59 g), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo, se añadió una solución de 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carbaldehído (10.0 g) en tetrahidrofurano (30 ml), y la mezcla se agitó durante 1 hora. La mezcla se calentó hasta

temperatura ambiente y luego se agitó durante 30 min. La mezcla de reacción se concentró, se añadió una solución acuosa saturada de cloruro de amonio al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:100 - 1:4, v/v) para dar (2E)-3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrilato de etilo (12.1 g, rendimiento: 100%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.96 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.40 - 1.55 (2 H, m), 1.69 - 1.80 (2 H, m), 4.12 (2 H, t, J = 6.6 Hz), 4.22 (2 H, q, J = 7.2 Hz), 5.33 (2 H, s), 6.02 (1 H, s), 6.28 (1 H, d, J = 15.8 Hz), 6.65 (1 H, d, J = 8.4 Hz), 7.15 (1 H, dd, J = 2.1, 8.4 Hz), 7.39 (1 H, d, J = 15.8 Hz), 7.40 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 129

Una mezcla de (2E)-3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrilato de etilo (8.00 g), paladio-carbón al 5% (1.00 g) y tetrahidrofurano (100 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró para dar 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoato de etilo (8.01 g, rendimiento: 60%) en forma de un aceite de color amarillo pálido.

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^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.95 (3 H, t, J = 7.3 Hz), 1.24 (3 H, t, J = 7.2 Hz), 1.38 - 1.54 (2 H, m), 1.66 - 1.78 (2 H, m), 2.52 - 2.64 (2 H, m), 2.72 - 2.82 (2 H, m), 4.09 (2 H, t, J = 6.7 Hz), 4.12 (2 H, q, J = 7.2 Hz), 5.19 (2 H, s), 5.54 (1 H, s), 6.54 (1 H, d, J = 8.3 Hz), 7.15 (1 H, dd, J = 2.1, 8.3 Hz), 7.38 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 130

A una solución (100 ml) de 2-hidroxi-4-(metoximetoxi)benzaldehído (11.9 g) en N,N-dimetilformamida se añadieron bromuro de bencilo (8.5 ml) y carbonato de potasio (10.8 g) a temperatura ambiente, y la mezcla se agitó a 80°C durante 1 hora. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró para dar un aceite. A una solución (150 ml) de dietilfosfonoacetato de etilo (15.0 ml) en tetrahidrofurano se añadió hidruro de sodio (60% en aceite, 3.3 g) a temperatura ambiente, y la mezcla se agitó durante 30 min. Una solución (50 ml) del aceite en tetrahidrofurano obtenida con anterioridad se añadió gota a gota a esta mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 hora. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió

a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5, v/v) para dar (2E)-3-[2-(benciloxi)-4-(metoximetoxi)fenil]acrilato de etilo en forma de un aceite amarillo (21.6 g, rendimiento: 96%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.32 (3 H, t, J = 7.2 Hz), 3.46 (3 H, s), 4.23 (2 H, q, J = 7.2 Hz), 5.14 (2 H, s), 5.16 (2 H, s), 6.44 (1 H, d, J = 16.2 Hz), 6.65 - 6.69 (2 H, m), 7.28 - 7.49 (6 H, m), 8.00 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 131

A una solución mixta de (2E)-3-[2-(benciloxi)-4-(metoximetoxi)fenil]acrilato de etilo (4.0 g) en tetrahidrofurano-etanol (1:1, v/v, 100 ml) se añadió paladio sobre carbón al 10% (0.5 g), y la mezcla se agitó bajo una atmósfera de hidrógeno durante 3 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:5, v/v) para dar 3-[2-hidroxi-4-(metoximetoxi)fenil]propanoato de etilo en forma de un aceite incoloro (2.8 g, rendimiento: 95%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.24 (3 H, t, J = 7.2 Hz), 2.62 - 2.71 (2 H, m), 2.78 - 2.89 (2 H, m), 3.46 (3 H, s), 4.15 (2 H, q, J = 7.2 Hz), 5.12 (2 H, s), 6.52 - 6.64 (2 H, m), 6.97 (1 H, d, J = 8.3 Hz), 7.42 (1 H, s).

Ejemplo de referencia 132

A una solución (30 ml) de 3-[2-hidroxi-4-

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(metoximetoxi)fenil]propanoato de etilo (1.27 g) en N,N-dimetilformamida se añadió hidruro de sodio (60% en aceite, 240 mg) a temperatura ambiente, y la mezcla se agitó durante 30 min. Se añadió 2.3-dicloro-5-(trifluorometil)piridina (0.80 ml) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 3 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:10, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propanoato de etilo en forma de un aceite incoloro (1.60 g, rendimiento: 74%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 2.52 - 2.64 (2 H, m), 2.71 - 2.83 (2 H, m), 3.47 (3 H, s), 4.09 (2 H, q, J = 7.2 Hz), 5.15 (2 H, s), 6.82 (1 H, d, J = 2.6 Hz), 6.93 (1 H, dd, J = 8.5, 2.5 Hz), 7.24 (1 H, d, J = 8.5 Hz), 7.97 - 8.00 (1 H, m), 8.22 - 8.30 (1 H, m).

Ejemplo de referencia 133

A una solución de alcohol 2-cloro-4-trifluorometilbencílico (38.8 g) y piridina (3.0 ml) en éter dietílico (320 ml)-tetrahidrofurano (80 ml) se añadió cloruro de tionilo (32.8 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La solución de reacción se concentró,

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se vertió agua en el residuo y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:25 - 1:12, v/v) para dar cloruro de 2-cloro-4-trifluorometilbencilo (38.9 g, rendimiento: 92%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:4.72 (2 H, s), 7.51 - 7.57 (1 H, m), 7.60 - 7.70 (2 H, m).

Ejemplo de referencia 134

Una solución (50 ml) de (2E)-3-[2-(benciloxi)-4-hidroxifenil]acrilato de etilo (5.1 g) en N,N-dimetilformamida se añadió 2-yodopropano (2.0 ml) y carbonato de potasio (3.1 g), y la mezcla se agitó a 60°C durante 1.5 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5, v/v) para dar (2E)-3-[2-(benciloxi)-4-isopropoxifenil]acrilato de etilo en forma de un aceite incoloro (5.0 g, rendimiento: 86%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.27 - 1.35 (9 H, m), 4.23 (2 H, q, J = 7.0 Hz), 4.46 - 4.61 (1 H, m), 5.13 (2 H, s),

6.38 - 6.54 (3 H, m), 7.28 - 7.51 (6 H, m), 8.00 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 135

A (2E)-3-[2-(benciloxi)-4-isopropoxifenil]acrilato de etilo (5.0 g) en una solución mixta de tetrahidrofurano-etanol (1:1, v/v, 100 ml) se añadió paladio sobre carbón al 10% (0.5 g), y la mezcla se agitó bajo una atmósfera de hidrógeno durante 2 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar 3-(2-hidroxi-4-isopropoxifenil)propanoato de etilo en forma de un aceite de color amarillo pálido (3.3 g, rendimiento: 89%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.24 (3 H, t, J = 7.2 Hz), 1.31 (6 H, d, J = 6.0 Hz), 2.63 - 2.72 (2 H, m), 2.76 - 2.86 (2 H, m), 4.15 (2 H, q, J = 7.2 Hz), 4.40 - 4.55 (1 H, m), 6.38 - 6.48 (2 H, m), 6.94 (1 H, d, J = 8.3 Hz), 7.43 (1 H, s).

Ejemplo de referencia 136

A una solución (60 ml) 3-(2-hidroxi-4-isopropoxifenil)propanoato de etilo (1.51 g) en N,N-dimetilformamida se añadió hidruro de sodio (60% en aceite, 312 mg) a temperatura ambiente, y la mezcla se agitó durante 30 min. Se añadió 2.3-dicloro-5-(trifluorometil)piridina (1.56 g) a esta mezcla de reacción, y la mezcla se agitó a 60°C

durante 15 min. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:15, v/v) para dar 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propanoato de etilo en forma de un aceite incoloro (2.02 g, rendimiento: 78%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 1.32 (6 H, d, J = 6.0 Hz), 2.52 - 2.62 (2 H, m), 2.70 - 2.81 (2 H, m), 4.09 (2 H, q, J = 7.2 Hz), 4.41 - 4.56 (1 H, m), 6.63 (1 H, d, J = 2.6 Hz), 6.76 (1 H, dd, J = 8.5, 2.6 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.27 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 137

A una mezcla de (2E)-3-[2-(benciloxi)-4-hidroxifenil]acrilato de etilo (2.5 g), 2-metoxietanol (1.0 ml), tributilfosfina (3.5 ml) y tetrahidrofurano (100 ml) se añadió 1.1'-azodicarbonildipiperidina (4.2 g) a temperatura ambiente, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:5,

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v/v) para dar (2E)-3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]acrilato de etilo en forma de un aceite incoloro (2.5 g, rendimiento: 83%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.31 (3 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.69 - 3.78 (2 H, m), 4.06 - 4.15 (2 H, m), 4.23 (2 H, q, J = 7.2 Hz), 5.13 (2 H, s), 6.37 - 6.58 (3 H, m), 7.28 - 7.51 (6 H, m), 7.99 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 138

A (2E)-3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.5 g) en una solución mixta de tetrahidrofurano-etanol (1:1, v/v, 100 ml) se añadió paladio sobre carbón al 10% (0.25 g), y la mezcla se agitó bajo una atmósfera de hidrógeno durante 3 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5 - 1:3, v/v) para dar 3-[2-hidroxi-4-(2-metoxietoxi)fenil]propanoato de etilo en forma de un aceite incoloro (2.8 g, rendimiento: 95%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.23 (3 H, t, J = 7.2 Hz), 2.62 - 2.70 (2 H, m), 2.78 - 2.86 (2 H, m), 3.44 (3 H, s), 3.70 - 3.75 (2 H, m), 4.04 - 4.09 (2 H, m), 4.14 (2 H, q, J = 7.2 Hz), 6.42 - 6.52 (2 H, m), 6.95 (1 H, d, J = 8.1 Hz), 7.42 - 7.50 (1 H, m).

Ejemplo de referencia 139

A una solución (40 ml) de 3-[2-hidroxi-4-(2-metoxietoxi)fenil]propanoato de etilo (1.6 g) en N,N-dimetilformamida se añadió hidruro de sodio (60% en aceite,

285 mg) a temperatura ambiente, y la mezcla se agitó durante 30 min. Se añadió 2.3-dicloro-5-(trifluorometil)piridina (0.9 ml) a esta mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 30 min. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanoato de etilo en forma de un aceite incoloro (2.2 g, rendimiento: 84%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 2.50 - 2.63 (2 H, m), 2.72 - 2.84 (2 H, m), 3.43 (3 H, s), 3.65 - 3.79 (2 H, m), 4.02 - 4.16 (4 H, m),6.68 (1 H, d, J = 2.6 Hz), 6.82 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.21 - 8.29 (1 H, m).

Ejemplo de referencia 140

A una solución (100 ml) de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanoato de etilo (2.2 g) en tetrahidrofurano se añadió hidruro de litio y aluminio (186 mg) a temperatura ambiente, y la mezcla se agitó durante 15 min. Se añadió sulfato de sodio decahidratado (1.6 g) a esta mezcla de reacción, y la mezcla se filtró a través de celite y

se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol en forma de un aceite incoloro (1.7 g, rendimiento: 83%). La recristalización en acetato de etilo-hexano dio cristales prismáticos incoloros. Punto de fusión 70°C-71°C.

Ejemplo de referencia 141

A una solución de 3-(3-isopropoxi-1H-pirazol-5-il)propionato de etilo (1.50 g) en N,N-dimetilformamida (20 ml) se añadió hidruro de sodio (60% en aceite, 290 mg) a temperatura ambiente, y la mezcla se agitó durante 10 min. Se agregó bromuro de 2,4-difluorobencilo (1.65 g) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:49 - 1:3, v/v) para dar 3-[1-(2,4-difluorobencil)-3-isopropoxi-1H-pirazol-5-il]propionato de etilo (660 mg, rendimiento: 28%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.24 (3 H, t, J = 7.2 Hz), 1.32 (6 H, d, J = 6.3 Hz), 2.52 - 2.62 (2 H, m), 2.77 - 2.87 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.60 - 4.76 (1 H, m),

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5.13 (2 H, s), 5.47 (1 H, s), 6.66 - 6.97 (3 H, m).

Ejemplo de referencia 142

Una mezcla de 3-isopropoxi-1H-pirazol-5-carboxilato de metilo (11.08 g), cloruro de 2,4-diclorobencilo (13.0 g), carbonato de potasio (10.00 g) y N,N-dimetilformamida (80 ml) se agitó durante la noche a temperatura ambiente. Se añadió agua (100 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (100 ml×2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:8 - 1:2, v/v) para dar 1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-carboxilato de metilo (Ejemplo de referencia 142a) (13.68 g, rendimiento: 66%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.34 (6 H, d, J = 5.8 Hz), 3.81 (3 H, s), 4.72 (1 H, septeto, J = 6.2 Hz), 5.67 (2 H, s), 6.28 (1 H, s), 6.54 (1 H, d, J = 8.4 Hz), 7.12 (1 H, dd, J = 8.4, 1.8 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Luego se obtuvo 1-(2,4-diclorobencil)-5-isopropoxi-1H-pirazol-3-carboxilato de metilo (Ejemplo de referencia 142b) (6.00 g, rendimiento: 29%) en forma de cristales incoloros. Punto de fusión 89-90°C.

Ejemplo de referencia 143

Una solución de 1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-carboxilato de metilo (13.68 g) en

tetrahidrofurano (40 ml) se añadió a una suspensión de hidruro de litio y aluminio (1.90 g) en tetrahidrofurano (70 ml) bajo enfriamiento con hielo durante 45 min, y la mezcla se agitó durante 30 min. Se añadieron etanol (20 ml) y luego una solución acuosa saturada de cloruro de amonio (7.0 ml) se añadieron a la mezcla de reacción, el producto inorgánico precipitado se filtró y se lavó con acetona. Se añadió acetato de etilo (100 ml) al residuo, y la mezcla se secó ($MgSO_4$), se filtró y se concentró para dar [1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]metanol en forma de cristales incoloros (12.05 g, rendimiento: 96%). Punto de fusión 89-90°C.

Ejemplo de referencia 144

Una solución de dimetilsulfóxido (10.8 ml) en diclorometano (100 ml) se enfrió hasta -70°C, se añadió cloruro de oxalilo (6.70 ml) durante 20 min, y la mezcla se agitó durante 20 min. Luego se añadió una solución de [1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]metanol (12.05 g) en diclorometano (15 ml) durante 20 min, y la mezcla se agitó durante 30 min. Se agregó trietilamina (29 ml) a la mezcla de reacción durante 10 min, y la mezcla se calentó gradualmente hasta temperatura ambiente. Se añadió ácido clorhídrico 1 N (100 ml) a la mezcla de reacción, la capa de diclorometano se separó y se concentró para dar un residuo. Por separado, la capa acuosa se extrajo con acetato de etilo (100 ml) y se combinó con el residuo antes obtenido. La capa orgánica se

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lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:6, v/v) para dar 1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-carbaldehído en forma de un aceite amarillo (11.37 g, rendimiento: 95%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.35 (6 H, d, J = 6.2 Hz), 4.76 (1 H, septeto, J = 6.1 Hz), 5.64 (2 H, s), 6.31 (1 H, s), 6.60 (1 H, d, J = 8.4 Hz), 7.13 (1 H, dd, J = 8.4, 2.2 Hz), 7.39 (1 H, d, J = 2.2 Hz), 9.74 (1 H, s).

Ejemplo de referencia 145

Una solución de 1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-carbaldehído (11.37 g) y dietilfosfonoacetato de etilo (8.95 g) en tetrahidrofurano (40 ml) se añadió a una suspensión de hidruro de sodio (60% en aceite, 1.75 g) en N,N-dimetilformamida (140 ml) bajo enfriamiento con hielo durante 40 min, y la mezcla se agitó a temperatura ambiente durante 30 min. Se añadió agua (200 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (100 ml x2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:6, v/v) para dar (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propenoato de etilo en forma de un aceite amarillo (12.78 g, rendimiento: 92%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.30 (3 H, t, J = 6.9 Hz), 1.34 (6 H, d, J = 6.2 Hz), 4.23 (2 H, q, J = 7.2 Hz), 4.72 (1 H, septeto, J = 6.4 Hz), 5.33 (2 H, s), 6.00 (1 H, s), 6.27 (1 H, d, J = 15.9 Hz), 6.66 (1 H, d, J = 8.4 Hz), 7.15 (1 H, dd, J = 8.2, 1.8 Hz), 7.35 - 7.45 (2 H, m).

Ejemplo de referencia 146

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propenoato de etilo (12.78 g), paladio-carbón al 5% (1.0 g) y tetrahidrofurano (80 ml) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 6 h. El catalizador se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:6, v/v) para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propionato de etilo en forma de un aceite de color amarillo pálido (11.37 g, rendimiento: 89%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.24 (3 H, t, J = 7.2 Hz), 1.33 (6 H, d, J = 6.2 Hz), 2.47 - 2.64 (2 H, m), 2.69 - 2.85 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.63 - 4.80 (1 H, m), 5.18 (2 H, s), 5.52 (1 H, s), 6.56 (1 H, d, J = 8.5 Hz), 7.15 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 147

Una mezcla de 3-(3-isopropil-1H-pirazol-5-il)propionato de etilo (1.22 g), cloruro de 2,4-diclorobencilo (0.82 ml), carbonato de potasio (0.75 g) y N,N-

dimetilformamida (10 ml) se agitó durante la noche a 80°C. Se añadió agua (15 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (20 ml×2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:7, v/v) para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propionato de etilo en forma de un aceite amarillo (1.12 g, rendimiento: 54%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.24 (3 H, t, J = 7.1 Hz), 1.33 (6 H, d, J = 5.8 Hz), 2.50 - 2.63 (2 H, m), 2.70 - 2.82 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.70 (1 H, septeto, J = 6.2 Hz), 5.18 (2 H, s), 5.52 (1 H, s), 6.56 (1 H, d, J = 8.0 Hz), 7.15 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Ejemplo de referencia 148

A una solución 1 N de borano en tetrahidrofurano (30 ml) se añadió ácido 2-cloro-4-trifluorometilbenzoico (2.50 g), y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se vertió en ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con una solución acuosa de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:4, v/v) para dar alcohol 2-

cloro-4-trifluorometilbencílico (2.23 g, rendimiento: 96%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:4.85 (2 H, d, J = 9.0 Hz), 7.52 - 7.80 (3 H, m).

Ejemplo de referencia 149

A una solución de alcohol 2-cloro-4-trifluorometilbencílico (2.23 g) y trifenilfosfina (4.17 g) en tetrahidrofurano (25 ml) se añadió tetrabromuro de carbono (5.27 g), y la mezcla se agitó a temperatura ambiente durante 2 h. La solución de reacción se concentró, se añadieron hexano y éter dietílico al residuo, y el material insoluble se filtró. El agua madre se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (0:1 - 1:4, v/v) para dar bromuro de 2-cloro-4-trifluorometilbencilo (2.90 g, rendimiento: 99%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:4.59 (2 H, s), 7.46 - 7.60 (2 H, m), 7.65 (1 H, s).

Ejemplo de referencia 150

A una solución de 3-(3-isopropoxi-1H-pirazol-5-il)propionato de etilo (1.50 g) en N,N-dimetilformamida (20 ml) se añadió hidruro de sodio (60% en aceite, 290 mg) a temperatura ambiente, y la mezcla se agitó durante 10 min. Se añadió bromuro de 2-cloro-4-trifluorometilbencilo (2.17 g) a la mezcla de reacción, y la mezcla se agitó a temperatura

ambiente durante 4 h. Se añadió ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:49 - 1:4, v/v) para dar 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}propionato de etilo (610 mg, rendimiento: 22%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.2 Hz), 1.32 (6 H, d, J = 6.3 Hz), 2.53 - 2.62 (2 H, m), 2.73 - 2.80 (2 H, m), 4.11 (2 H, q, J = 7.2 Hz), 4.64 - 4.76 (1 H, m), 5.25 (2 H, s), 5.54 (1 H, s), 6.69 (1 H, d, J = 7.8 Hz), 7.41 (1 H, d, J = 7.8 Hz), 7.62 (1 H, s).

Ejemplo de referencia 151

A una mezcla de ter-butóxido de potasio (55.1 g) en tetrahidrofurano (300 ml) se añadió una mezcla de 3-metilbutan-2-ona (30.0 g) y oxalato de dietilo (51.0 g) a temperatura ambiente durante 1 h. La mezcla se agitó durante la noche a temperatura ambiente, se añadieron ácido acético (47.7 ml) y monohidrato de hidracina (19.0 g), y la mezcla se agitó con calentamiento a reflujo durante 2 h. La mezcla de reacción se concentró, se añadió agua (200 ml), y la mezcla se extrajo con acetato de etilo (150 mlx2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de

sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar 3-isopropil-1H-pirazol-5-carboxilato de etilo en forma de un aceite marrón (31.82 g, rendimiento: 50%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.30 (6 H, d, J = 7.0 Hz), 1.38 (3 H, t, J = 7.2 Hz), 3.04 (1 H, septeto, J = 6.8 Hz), 4.37 (2 H, q, J = 6.8 Hz), 4.37 (2 H, q, J = 7.1 Hz), 6.63 (1 H, d, J = 0.6 Hz).

Ejemplo de referencia 152

Se agitaron 3-isopropil-1H-pirazol-5-carboxilato de etilo (10.00 g), cloruro de 2,4-diclorobencilo (11.8 g), carbonato de potasio (9.0 g) y N,N-dimetilformamida (50 ml) durante la noche a temperatura ambiente. Se añadió agua (80 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (50 mlx2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:15 - 1:4, v/v) para dar 1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-carboxilato de etilo (Ejemplo de referencia 152a) en forma de un aceite marrón (10.52 g, rendimiento: 56%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (6 H, d, J = 6.8 Hz), 1.29 (3 H, t, J = 7.1 Hz), 3.02 (1 H, septeto, J = 6.9 Hz), 4.26 (2 H, q, J = 7.1 Hz), 5.77 (2 H, s), 6.34 (1 H, d, J = 8.6 Hz), 6.78 (1 H, s), 7.09 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Luego se obtuvo 1-(2,4-diclorobencil)-5-isopropil-1H-pirazol-3-carboxilato de etilo (Ejemplo de referencia 152b) (8.73 g, rendimiento: 47%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.18 (6 H, d, J = 7.0 Hz), 1.40 (3 H, t, J = 7.1 Hz), 2.79 (1 H, septeto, J = 6.8 Hz), 4.42 (2 H, q, J = 7.2 Hz), 5.46 (2 H, s), 6.49 (1 H, d, J = 8.0 Hz), 6.70 (1 H, s), 7.13 (1 H, dd, J = 8.4, 2.2 Hz), 7.40 (1 H, d, J = 1.8 Hz).

Ejemplo de referencia 153

A una solución de 1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-carboxilato de etilo (10.52 g) en tetrahidrofurano (100 ml) se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (51.5 ml) durante 30 min bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 30 min, y se añadieron etanol (30 ml) y luego una solución acuosa saturada de cloruro de amonio (13 ml) a la solución de reacción. La sustancia inorgánica precipitada se filtró y se lavó con acetona. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar un [1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]metanol en forma de cristales incoloros (7.90 g, rendimiento: 86%). Punto de fusión 89-90°C.

Ejemplo de referencia 154

Una solución de dimetilsulfóxido (7.50 ml) en

diclorometano (100 ml) se enfrió hasta -70°C, se añadió cloruro de oxalilo (4.60 ml) durante 15 min, y la mezcla se agitó durante 15 min. Luego se añadió una solución de [1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]metanol (7.90 g) en diclorometano (25 ml) durante 20 min, y la mezcla se agitó durante 20 min. Se añadió trietilamina (20.0 ml) a la mezcla de reacción durante 10 min, y la mezcla se calentó lentamente hasta temperatura ambiente. La mezcla de reacción se concentró, y la sal precipitada se filtró y se lavó con éter diisopropílico. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:15 - 1:6, v/v) para dar 1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-carbaldehído en forma de un aceite amarillo (7.08 g, rendimiento: 90%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.30 (6 H, d, J = 7.0 Hz), 3.05 (1 H, septeto, J = 6.9 Hz), 5.75 (2 H, s), 6.42 (1 H, d, J = 8.6 Hz), 6.81 (1 H, s), 7.10 (1 H, dd, J = 8.2, 2.0 Hz), 7.39 (1 H, d, J = 2.2 Hz), 9.79 (1 H, s).

Ejemplo de referencia 155

Una solución de 1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-carbaldehído (7.08 g) y dietilfosfonoacetato de etilo (5.87 g) en tetrahidrofurano (15 ml) se añadió a una suspensión de hidruro de sodio (60% en aceite, 1.15 g) en N,N-dimetilformamida (40 ml) bajo enfriamiento con hielo durante

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20 min, y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió agua (80 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (40 mlx2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar (2E)-3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]propenoato de etilo en forma de un aceite amarillo (7.07 g, rendimiento: 81%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.22 - 1.37 (9 H, m), 2.99 (1 H, septeto, J = 6.9 Hz), 4.22 (2 H, q, J = 7.2 Hz), 5.44 (2 H, s), 6.30 (1 H, d, J = 15.8 Hz), 6.44 - 6.53 (2 H, m), 7.13 (1 H, dd, J = 8.2, 2.0 Hz), 7.40 (1 H, d, J = 2.2 Hz), 7.41 (1 H, d, J = 15.8 Hz).

Ejemplo de referencia 156

Una mezcla de (2E)-3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]propenoato de etilo (7.07 g), paladio-carbón al 5% (1.4 g) y tetrahidrofurano (45 ml) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 4 h. El catalizador se filtró, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:6, v/v) para dar 3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]propionato de etilo en forma de un aceite incoloro (5.36 g, rendimiento: 76%).

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.20 - 1.32 (9 H, m), 2.53 - 2.65 (2 H, m), 2.72 - 2.85 (2 H, m), 2.96 (1 H, septeto, J = 7.0 Hz), 4.13 (2 H, q, J = 7.2 Hz), 5.30 (2 H, s), 5.94 (1 H, s), 6.38 (1 H, d, J = 8.4 Hz), 7.13 (1 H, dd, J = 8.4, 2.2 Hz), 7.38 (1 H, d, J = 2.2 Hz).

Ejemplo de referencia 157

A una solución de 3-isopropil-1H-pirazol-5-carboxilato de etilo (4.39 g) y cloruro de 2-cloro-4-trifluorobencilo (6.07 g) en N,N-dimetilformamida (70 ml) se añadió carbonato de potasio (3.99 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:49 - 1:4, v/v) para dar 1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-carboxilato de etilo (3.80 g, rendimiento: 42%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.1 Hz), 1.30 (6 H, d, J = 7.0 Hz), 2.91 - 3.10 (1 H, m), 4.26 (2 H, q, J = 7.1 Hz), 5.85 (2 H, s), 6.48 (1 H, d, J = 8.1 Hz), 6.80 (1 H, s), 7.38 (1 H, d, J = 8.1 Hz), 7.64 (1 H, s).

Ejemplo de referencia 158

A una solución de 1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-carboxilato de etilo (3.80 g) en tetrahidrofurano (50 ml) se añadió una

solución toluénica 1.5 M de hidruro de diisobutilaluminio (17 ml) a 0°C. Tras agitar a temperatura ambiente durante 1 h, se añadió metanol para neutralizar la reacción. Se añadió una solución acuosa de sal de Rochelle al 10% (200 ml), y la mezcla se agitó durante 4 horas y se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar {1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}metanol (3.37 g, rendimiento: 99%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (6 H, d, J = 6.9 Hz), 1.63 (1 H, t, J = 5.6 Hz), 2.92 - 3.06 (1 H, m), 4.57 (1 H, d, J = 5.6 Hz), 5.49 (2 H, s), 6.14 (1 H, s), 6.59 (1 H, d, J = 8.0 Hz), 7.39 (1 H, dd, J = 1.2, 8.0 Hz), 7.62 (1 H, d, J = 1.2 Hz).

Ejemplo de referencia 159

Bajo una atmósfera de nitrógeno, a una solución de cloruro de oxalilo (2.56 g) en cloruro de metileno (50 ml) se añadió dimetilsulfóxido (2.15 ml) a -78°C. Tras agitar a -78°C durante 5 min, se añadió una solución de {1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}metanol (3.37 g) en cloruro de metileno (35 ml). Tras agitar a -78°C durante 1 hora, se añadió trietilamina (5.11 g). La mezcla de

reacción se agitó a temperatura ambiente durante 1 hora y se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v) para dar 1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-carbaldehído (3.32 g, rendimiento: 99%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.31 (6 H, d, J = 7.2 Hz), 2.98 - 3.13 (1 H, m), 5.82 (2 H, s), 6.52 (1 H, d, J = 8.1 Hz), 6.83 (1 H, s), 7.36 (1 H, dd, J = 1.2, 8.1 Hz), 7.65 (1 H, d, J = 1.2 Hz), 9.79 (1 H, s).

Ejemplo de referencia 160

Bajo enfriamiento con hielo, a una suspensión de hidruro de sodio (60% en aceite, 560 mg) en N,N-dimetilformamida (30 ml) se añadió una solución mixta de 1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-carbaldehído (3.32 g) y dietilfosfonoacetato de etilo (2.69 g) en tetrahidrofurano (15 ml). Tras agitar a temperatura ambiente durante 1.5 h, la mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de

gel de sílice, y se eluyó con acetato de etilo-hexano (1:49 - 3:17, v/v) para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}acrilato de etilo (1.18 g, rendimiento: 29%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.28 (6 H, d, J = 6.9 Hz), 1.30 (3 H, t, J = 7.2 Hz), 2.93 - 3.07 (1 H, m), 4.21 (2 H, q, J = 7.2 Hz), 5.51 (2 H, s), 6.31 (1 H, d, J = 15.8 Hz), 6.50 (1 H, s), 6.60 (1 H, d, J = 7.8 Hz), 7.38 (1 H, d, J = 15.8 Hz), 7.40 (1 H, d, J = 7.8 Hz), 7.65 (1 H, s).

Ejemplo de referencia 161

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}acrilato de etilo (1.18 g), paladio-carbón al 5% (290 mg) y tetrahidrofurano (15 ml) se hidrogenó a temperatura ambiente a presión atmosférica. La mezcla de reacción se filtró, y el filtrado se concentró para dar 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}propionato de etilo (1.00 g, rendimiento: 84%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.2 Hz), 1.26 (6 H, d, J = 7.2 Hz), 2.57 - 2.64 (2 H, m), 2.74 - 2.81 (2 H, m), 2.89 - 3.02 (1 H, m), 4.11 (2 H, q, J = 7.2 Hz), 5.38 (2 H, s), 5.96 (1 H, s), 6.51 (1 H, d, J = 8.1 Hz), 7.40 (1 H, dd, J = 1.2, 8.1 Hz), 7.63 (1 H, d, J = 1.2 Hz).

Ejemplo de referencia 162

A una mezcla de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (0.98 g), ciclohexanol (0.48 g), tributilfosfina (0.89 g) y tetrahidrofurano (10 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.03 g) a temperatura ambiente, y la mezcla se agitó durante 6 h. Se agregaron tributilfosfina (0.89 g) y 1.1'-(azodicarbonil)dipiperidina (1.03 g) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó a 50°C durante 24 h. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (3:17 - 3:7, v/v) para dar (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]acrilato de etilo en forma de un aceite incoloro (0.80 g, rendimiento: 83%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.26 - 1.44 (7 H, m), 1.46 - 1.70 (4 H, m), 1.70 - 2.04 (4 H, m), 3.45 (3 H, s), 3.73 - 3.76 (2 H, m), 4.11 - 4.14 (2 H, m), 4.20 - 4.32 (3 H, m), 6.38 - 6.52 (3 H, m), 7.42 (1 H, d, J = 8.7 Hz), 7.93 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 163

Una mezcla de (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (0.80 g), paladio sobre carbón al 10% (0.15 g) y tetrahidrofurano (35 ml) se agitó

bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. El catalizador se filtró, y el filtrado se concentró para dar 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propanoato de etilo en forma de un aceite de color negro pálido (0.80 g, rendimiento: 99%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.23 (3 H, t, J = 7.2 Hz), 1.30 - 1.62 (6 H, m), 1.70 - 1.98 (4 H, m), 2.54 - 2.59 (2 H, m), 2.83 - 2.88 (2 H, m), 3.44 (3 H, s), 3.71 - 3.74 (2 H, m), 4.06 - 4.14 (4 H, m), 4.20 - 4.28 (1 H, m), 6.36 (1 H, dd, J = 8.4, 2.4 Hz), 6.48 (1 H, d, J = 2.4 Hz), 7.01 (1 H, d, J = 8.1 Hz).

Ejemplo de referencia 164

Se disolvió 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propanoato de etilo (0.80 g) en tetrahidrofurano (20 ml), se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (6.1 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadieron sulfato de sodio decahidratado (2.95 g) y éter dietílico (50 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. El sólido resultante se filtró y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 2:3, v/v) para dar 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propan-1-ol en forma de un aceite incoloro (0.63 g, rendimiento: 90%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.24 - 1.42 (2 H, m), 1.44 - 1.60 (4 H, m), 1.72 - 1.84 (4 H, m), 1.96 - 2.00 (3 H, m), 2.66 (2 H, t, J = 6.9 Hz), 3.45 (3 H, s), 3.55 (2 H, q, J = 6.0 Hz), 3.72 - 3.75 (2 H, m), 4.07 - 4.10 (2 H, m), 4.20 - 4.28 (1 H, m), 6.42 (1 H, dd, J = 8.1, 2.4 Hz), 6.52 (1 H, d, J = 2.4 Hz), 7.01 (1 H, d, J = 8.1 Hz).

Ejemplo de referencia 165

Una mezcla de (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (1.18 g), paladio sobre carbón al 10% (0.25 g) y tetrahidrofurano (50 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. El catalizador se filtró, y el filtrado se concentró para dar 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propanoato de etilo en forma de un aceite incoloro (1.18 g, rendimiento: 98%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.32 - 0.34 (2 H, m), 0.59 - 0.62 (2 H, m), 1.21 - 1.30 (4 H, m), 2.56 - 2.62 (2 H, m), 2.89 (2 H, t, J = 7.8 Hz), 3.44 (3 H, s), 3.71 - 3.74 (2 H, m), 3.78 (2 H, d, J = 6.6 Hz), 4.07 - 4.15 (4 H, m), 6.39 (1 H, dd, J = 8.1, 2.4 Hz), 6.45 (1 H, d, J = 2.4 Hz), 7.02 (1 H, d, J = 8.1 Hz).

Ejemplo de referencia 166

Se disolvió 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propanoato de etilo (1.18 g) en tetrahidrofurano (30 ml), se añadió una solución de hidruro de

diisobutilaluminio 1.5 M en tolueno (10 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 40 min. Se añadieron sulfato de sodio decahidratado (4.83 g) y éter dietílico (60 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. El sólido resultante se filtró y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 9:11, v/v) para dar 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propan-1-ol en forma de un aceite incoloro (0.99 g, rendimiento: 94%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.32 - 0.38 (2 H, m), 0.60 - 0.66 (2 H, m), 1.22 - 1.32 (1 H, m), 1.76 - 1.84 (2 H, m), 2.14 (1 H, t, J = 6.3 Hz), 2.70 (2 H, t, J = 6.6 Hz), 3.44 (3 H, s), 3.55 (2 H, q, J = 6.0 Hz), 3.71 - 3.75 (2 H, m), 3.78 (2 H, d, J = 6.9 Hz), 4.07 - 4.10 (2 H, m), 6.42 - 6.46 (2 H, m), 7.01 (1 H, d, J = 8.1 Hz).

Ejemplo de referencia 167

Una mezcla de (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]acrilato de etilo (1.05 g), paladio sobre carbón al 10% (0.20 g) y tetrahidrofurano (40 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. El catalizador se filtró, y el filtrado se concentró para dar 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propanoato de etilo en forma de un aceite incoloro (1.18 g, rendimiento: 98%).

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^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.20 - 1.25 (3 H, m), 1.80 - 2.12 (4 H, m), 2.53 - 2.59 (2 H, m), 2.84 - 2.90 (2 H, m), 3.39 (3 H, s), 3.71 - 3.74 (2 H, m), 3.79 - 3.85 (1 H, m), 3.86 - 4.00 (3 H, m), 4.06 - 4.14 (4 H, m), 4.23 - 4.30 (1 H, m), 6.40 (1 H, dd, J = 8.1, 2.4 Hz), 6.48 (1 H, d, J = 2.4 Hz), 7.02 (1 H, d, J = 8.4 Hz).

Ejemplo de referencia 168

3-[4-(2-Metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propanoato de etilo (1.04 g) se disolvió en tetrahidrofurano (24 ml), se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (8.0 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 20 min. Se agregaron sulfato de sodio decahidratado (3.87 g) y éter dietílico (70 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. El sólido resultante se filtró y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 1:1, v/v) para dar 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propan-1-ol en forma de un aceite incoloro (0.50 g, rendimiento: 54%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.66 - 2.12 (6 H, m), 2.58 - 2.67 (2 H, m), 2.72 - 2.82 (1 H, m), 3.44 (3 H, s), 3.51 (2 H, q, J = 5.7 Hz), 3.72 - 3.75 (2 H, m), 3.80 - 4.00 (4 H, m), 4.07 - 4.11 (2 H, m), 4.24 - 4.32 (1 H, m), 6.43 - 6.48 (2 H, m), 7.02 (1 H, d, J = 8.4 Hz).

Ejemplo de referencia 169

A una solución (400 ml) de 2,4-dihidroxibenzaldehído (30.0 g), 2-metoxietanol (21.4 g) y trifenilfosfina (74.0 g) en tolueno se añadió gota a gota una solución toluénica al 40% de dietilazodicarboxilato de metilo (128 ml) a 0°C durante aproximadamente 25 min, y la mezcla se calentó hasta temperatura ambiente y se agitó durante 90 min. La mezcla de reacción se concentró, y el residuo se mezcló con acetato de etilo, el material insoluble se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:5 - 1:2, v/v) para dar 2-hidroxi-4-(2-metoxietoxi)benzaldehído (14.7 g, rendimiento: 34%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:3.45 (3 H, s), 3.74 - 3.78 (2 H, m), 4.15 - 4.18 (2 H, m), 6.44 (1 H, d, J = 2.4 Hz), 6.57 (1 H, dd, J = 8.7, 2.4 Hz), 7.42 (1 H, d, J = 8.7 Hz), 9.71 (1 H, s), 11.46 (1 H, s).

Ejemplo de referencia 170

A una solución (200 ml) de 2-hidroxi-4-(2-metoxietoxi)benzaldehído (11.4 g) en tetrahidrofurano se añadió [(etoxicarbonil)metilen]trifenilfosforano (22.2 g) a 0°C, y la mezcla se calentó hasta temperatura ambiente y se agitó durante 4 h. La mezcla de reacción se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (2:3, v/v). Los

cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (15.7 g, rendimiento: 82%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.33 (3 H, t, J = 7.2 Hz), 3.47 (3 H, s), 3.76 - 3.78 (2 H, m), 4.10 - 4.13 (2 H, m), 4.26 (2 H, q, J = 7.2 Hz), 6.44 - 6.52 (3 H, m), 7.09 (1 H, s), 7.37 (1 H, d, J = 9.3 Hz), 7.92 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 171

A una solución mixta de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (2.00 g) en acetonitrilo (20 ml) y N,N-dimetilformamida (10 ml) se añadieron bromometilciclohexano (4.04 g), carbonato de potasio (3.10 g) y yoduro de sodio (2.37 g), y la mezcla se calentó a reflujo durante 40 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar (2E)-3-[2-(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.22 g, rendimiento: 81%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.07 - 1.38 (8 H, m), 1.75 - 1.90 (6 H, m), 3.45 (3 H, s), 3.75 - 3.79 (4 H, m), 4.12 - 4.15 (2 H, m), 4.24 (2 H, q, J = 7.2 Hz), 6.40 - 6.49 (3 H,

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m), 7.43 (1 H, d, J = 9.3 Hz), 7.93 (1 H, d, J = 15.9 Hz).

Ejemplo de referencia 172

A una solución mixta de (2E)-3-[2-(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.21 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (12 ml), y la mezcla se agitó a 60°C durante 3 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]acrílico (1.91 g, rendimiento: 93%) en forma de cristales incoloros. Punto de fusión 111.5-112.5°C.

Ejemplo de referencia 173

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (2.00 g) en N,N-dimetilformamida (10 ml) se añadieron (bromometil)ciclopropano (1.57 g) y carbonato de potasio (2.07 g), y la mezcla se agitó a temperatura ambiente durante 20 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido

se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.03 g, rendimiento: 84%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.33 - 0.38 (2 H, m), 0.63 - 0.69 (2 H, m), 1.29 - 1.36 (4 H, m), 3.45 (3 H, s), 3.72 - 3.76 (2 H, m), 3.83 (2 H, d, J = 6.9 Hz), 4.09 - 4.13 (2 H, m), 4.24 (2 H, q, J = 7.2 Hz), 6.45 - 6.51 (3 H, m), 7.43 (1 H, d, J = 8.4 Hz), 7.94 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 174

A una solución mixta de (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.02 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (13 ml), y la mezcla se agitó a 60°C durante 2 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]acrílico (1.85 g, rendimiento: 99%) en forma de cristales incoloros. Punto de fusión 117.8-118.8°C.

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Ejemplo de referencia 175

A una solución mixta de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (2.00 g), 1-Boc-4-hidroxipiperidina (2.30 g) y tributilfosfina (4.58 g) en tolueno (260 ml) y tetrahidrofurano (10 ml) se añadió lentamente 1.1'-(azodicarbonil)dipiperidina (5.28 g) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 30 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, luego se vertió también agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. Se agregó un solvente mixto de acetato de etilo-hexano (1:1, v/v) al residuo obtenido, y el material insoluble se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (2:3, v/v) para dar 4-[2-[(1E)-3-etoxi-3-oxoprop-1-en-1-il]-5-(2-metoxietoxi)fenoxi]piperidin-1-carboxilato de ter-butilo (2.54 g, rendimiento: 75%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.32 (3 H, t, J = 7.2 Hz), 1.47 (9 H, s), 1.76 - 1.86 (2 H, m), 1.87 - 1.99 (2 H, m), 3.37 - 3.50 (5 H, m), 3.64 - 3.76 (4 H, m), 4.12 - 4.14 (2 H, m), 4.24 (2 H, q, J = 7.2 Hz), 4.48 - 4.52 (1 H, m), 6.39 (1 H, d, J = 16.2 Hz), 6.50 - 6.52 (2 H, m), 7.44 - 7.47 (1 H, m), 7.91 (1 H, d, J = 16.2 Hz).

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Ejemplo de referencia 176

A una solución mixta de 4-[2-[(1E)-3-etoxi-3-oxoprop-1-en-1-il]-5-(2-metoxietoxi)fenoxi]piperidin-1-carboxilato de ter-butilo (2.54 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (11.3 ml), y la mezcla se agitó a 60°C durante 90 min. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar ácido (2E)-3-[2-{[1-(ter-butoxicarbonil)piperidin-4-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (2.28 g, rendimiento: 95%) en forma de un sólido amorfo de color amarillo pálido.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:1.40 (9 H, s), 1.55 - 1.61 (2 H, m), 1.85 - 1.95 (2 H, m), 3.20 - 3.31 (5 H, m), 3.57 - 3.65 (4 H, m), 4.12 - 4.15 (2 H, m), 4.69 - 4.76 (1 H, m), 6.38 (1 H, d, J = 16.2 Hz), 6.57 (1 H, dd, J = 8.4, 2.1 Hz), 6.71 (1 H, d, J = 2.1 Hz), 7.61 (1 H, d, J = 8.4 Hz), 7.75 (1 H, d, J = 16.2 Hz), 12.09 (1 H, brs).

Ejemplo de referencia 177

A una solución mixta de (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.07 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una

solución acuosa 1 N de hidróxido de sodio (12 ml), y la mezcla se agitó a 60°C durante 90 min. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]acrílico (1.59 g, rendimiento: 83%) en forma de cristales incoloros. Punto de fusión 102.0-113.6°C.

Ejemplo de referencia 178

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (2.70 g) en N,N-dimetilformamida (22 ml) se añadieron bromuro de tetrahidrofurfurilo (8.58 g), yoduro de sodio (7.56 g) y carbonato de potasio (6.97 g), y la mezcla se agitó a 80°C durante 170 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]acrilato de etilo (2.65 g, rendimiento: 75%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.31 (3 H, t, J = 7.2 Hz),

1.80 - 2.14 (4 H, m), 3.45 (3 H, s), 3.73 - 3.76 (2 H, m), 3.82 - 3.88 (1 H, m), 3.90 - 4.08 (3 H, m), 4.12 - 4.14 (2 H, m), 4.23 (2 H, q, J = 7.2 Hz), 4.30 - 4.35 (1 H, m), 6.42 (1 H, d, J = 16.2 Hz), 6.50 - 6.52 (2 H, m), 7.42 (1 H, d, J = 9.0 Hz), 7.91 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 179

A una solución mixta de (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]acrilato de etilo (2.65 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (15 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró y se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]acrílico en forma de cristales incoloros (1.99 g, rendimiento: 81%). Punto de fusión 106.1-107.7°C.

Ejemplo de referencia 180

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (1.40 g) en N,N-dimetilformamida (15 ml) se añadieron cloruro de 2,4-diclorobencilo (1.59 g) y carbonato de potasio (1.45 g), y la mezcla se agitó a temperatura ambiente durante 60 h. Se vertió

agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (2.07 g, rendimiento: 92%) en forma de cristales incoloros. Punto de fusión 100.8-101.1°C.

Ejemplo de referencia 181

A una solución mixta de (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (1.95 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (9 ml), y la mezcla se agitó a 60°C durante 90 min. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en éter diisopropílico-metanol para dar ácido (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]acrílico (1.80 g, rendimiento: 99%) en forma de cristales incoloros. Punto de fusión 175.6-177.5°C.

Ejemplo de referencia 182

A una solución de (2E)-3-[2-hidroxi-4-(2-

metoxietoxi)fenil]acrilato de etilo (900 mg) en N,N-dimetilformamida (15 ml) se añadió hidruro de sodio (60% en aceite, 188 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió 2.3,5-tricloropiridina (925 mg) a la mezcla de reacción, y la mezcla se agitó a 80°C durante 36 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (1.01 g, rendimiento: 72%) en forma de cristales incoloros. Punto de fusión 70.7-71.3°C.

Ejemplo de referencia 183

A una solución mixta de (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (1.45 g) en tetrahidrofurano (15 ml) y etanol (15 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (7 ml), y la mezcla se agitó a 60°C durante 1 hora. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se

secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en tetrahidrofurano-hexano para dar ácido (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrílico (1.24 g, rendimiento: 92%) en forma de cristales incoloros. Punto de fusión 182.3-184.0°C.

Ejemplo de referencia 184

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (1.20 g) en N,N-dimetilformamida (15 ml) se añadieron 4-(clorometil)-5-metil-2-fenil-1.3-oxazol (1.03 g) y carbonato de potasio (1.24 g), y la mezcla se agitó a temperatura ambiente durante 40 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}acrilato de etilo (1.85 g, rendimiento: 94%) en forma de cristales incoloros. Punto de fusión 109.4-110.0°C.

Ejemplo de referencia 185

A una solución mixta de (2E)-3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}acrilato de etilo (1.73 g) en tetrahidrofurano (15 ml) y etanol (15 ml) se

añadió una solución acuosa 1 N de hidróxido de sodio (12 ml), y la mezcla se agitó a 60°C durante 6 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en tetrahidrofurano-hexano para dar ácido (2E)-3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}acrílico (1.56 g, rendimiento: 96%) en forma de cristales incoloros. Punto de fusión 194.3-195.8°C.

Ejemplo de referencia 186

A una solución mixta de (2E)-3-{4-(2-metoxietoxi)-2-[2-nitro-5-(trifluorometil)fenoxi]fenil}acrilato de etilo (1.01 g) en tetrahidrofurano (5 ml) y etanol (5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (5 ml), y la mezcla se agitó a 70°C durante 2 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-3-{4-(2-metoxietoxi)-2-[2-nitro-5-(trifluorometil)fenoxi]fenil}acrílico (0.58 g, rendimiento: 61%) en forma de cristales incoloros.

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^{1}H-RMN (300 MHz, DMSO-d_6) δ:3.25 (3 H, s), 3.57 - 3.62 (2 H, m), 4.04 - 4.11 (2 H, m), 6.38 - 6.92 (3 H, m), 7.46 - 7.90 (4 H, m), 8.32 - 8.35 (1 H, m), 12.09 (1 H, brs).

Ejemplo de referencia 187

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (1.19 g) en N,N-dimetilformamida (8 ml) se añadieron 3-cloro-4-fluorobenzotrifluoruro (1.06 g) y carbonato de potasio (1.23 g), y la mezcla se agitó a 80°C durante 55 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar (2E)-3-[2-[2-cloro-4-(trifluorometil)fenoxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (1.76 g, rendimiento: 88%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.2 Hz), 3.41 (3 H, s), 3.69 - 3.72 (2 H, m), 4.05 - 4.09 (2 H, m), 4.22 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 2.4 Hz), 6.43 (1 H, d, J = 16.2 Hz), 6.77 (1 H, dd, J = 8.7, 2.4 Hz), 6.96 (1 H, d, J = 8.7 Hz), 7.45 (1 H, d, J = 8.7 Hz), 7.59 (1 H, d, J = 8.7 Hz), 7.75 (1 H, s), 7.85 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 188

A una solución mixta de (2E)-3-[2-[2-cloro-4-

(trifluorometil)fenoxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (1.76 g) en tetrahidrofurano (8 ml) y etanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (8 ml), y la mezcla se agitó a 50°C durante 90 min. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-[2-cloro-4-(trifluorometil)fenoxi]-4-(2-metoxietoxi)fenil]acrílico (1.60 g, rendimiento: 97%) en forma de cristales incoloros. Punto de fusión 165.6-166.0°C.

Ejemplo de referencia 189

A una solución de (2E)-3-(4-(2-metoxietoxi)-2-{[(trifluorometil)sulfonil]oxi}fenil)acrilato de etilo (1.50 g) en tetrahidrofurano (20 ml) se añadieron 4-aminobenzotrifluoruro (948 mg), 2.2'-bis(difenilfosfino)-1.1'-binaftilo racémico (282 mg), acetato de paladio (67 mg) y carbonato de cesio (1.83 g), y la mezcla se calentó a reflujo durante 16 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con

acetato de etilo-hexano (1:4, v/v) para dar (2E)-3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)acrilato de etilo (1.00 g, rendimiento: 65%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.1 Hz), 3.43 (3 H, s), 3.73 - 3.77 (2 H, m), 4.07 - 4.10 (2 H, m), 4.23 (2 H, q, J = 7.1 Hz), 5.85 (1 H, s), 6.31 (1 H, d, J = 15.7 Hz), 6.69 - 6.73 (1 H, m), 6.88 (1 H, d, J = 2.4 Hz), 6.98 (2 H, d, J = 8.7 Hz), 7.47 - 7.56 (3 H, m), 7.82 (1 H, d, J = 15.7 Hz).

Ejemplo de referencia 190

A una solución mixta de (2E)-3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)acrilato de etilo (1.42 g) en tetrahidrofurano (8 ml) y etanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (7 ml), y la mezcla se agitó a 50°C durante 2 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)acrílico (0.96 g, rendimiento: 72%) en forma de cristales amarillos.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:3.29 (3 H, s), 3.62 -

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3.65 (2 H, m), 4.05 - 4.16 (2 H, m), 6.33 - 6.43 (2 H, m), 6.77 - 6.98 (3 H, m), 7.48 - 7.80 (4 H, m), 8.60 (1 H, s), 12.12 (1 H, s).

Ejemplo de referencia 191

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (1.48 g) en N,N-dimetilformamida (10 ml) se añadieron 2.5-dibromotiazol (1.61 g) y carbonato de potasio (1.53 g), y la mezcla se agitó a 80°C durante 22 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar (2E)-3-[2-[(5-bromo-1.3-tiazol-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (1.69 g, rendimiento: 71%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.31 (3 H, t, J = 7.2 Hz), 3.43 (3 H, s), 3.73 - 3.75 (2 H, m), 4.10 - 4.14 (2 H, m), 4.23 (2 H, q, J = 7.2 Hz), 6.37 (1 H, d, J = 16.1 Hz), 6.83 (1 H, s), 6.87 (1 H, d, J = 8.7 Hz), 7.16 (1 H, s), 7.60 (1 H, d, J = 8.7 Hz), 7.79 (1 H, d, J = 16.1 Hz).

Ejemplo de referencia 192

A una solución mixta de (2E)-3-[2-[(5-bromo-1.3-tiazol-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo

(1.67 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (8 ml), y la mezcla se agitó a 50°C durante 30 min. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-3-[2-[(5-bromo-1.3-tiazol-2-il)oxi]-4-(2-metoxietoxi)fenil]acrílico (1.46 g, rendimiento: 93%) en forma de cristales incoloros. Punto de fusión 144.0-145.1°C.

Ejemplo de referencia 193

A una solución de (2E)-3-(4-(2-metoxietoxi)-2-{[(trifluorometil)sulfonil]oxi}fenil)acrilato de etilo (1.66 g) en tetrahidrofurano (20 ml) se añadieron 2-cloro-4-(trifluorometil)anilina (1.89 g), 2.2'-bis(difenilfosfino)-1.1'-binaftilo racémico (519 mg), acetato de paladio (140 mg) y carbonato de cesio (2.06 g), y la mezcla se calentó a reflujo durante 8 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar (2E)-3-[2-{[2-

cloro-4-(trifluorometil)fenil]amino}-4-(2-metoxietoxi)fenil]acrilato de etilo (1.00 g, rendimiento: 54%) en forma de cristales amarillos.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.29 (3 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.73 - 3.79 (2 H, m), 4.16 - 4.27 (4 H, m), 6.23 (1 H, s), 6.34 (1 H, d, J = 15.9 z), 6.55 - 6.59 (1 H, m), 6.85 - 6.91 (2 H, m), 7.32 - 7.62 (3 H, m), 7.77 (1 H, d, J = 15.9 Hz).

Ejemplo de referencia 194

A una solución mixta de (2E)-3-[2-{[2-cloro-4-(trifluorometil)fenil]amino}-4-(2-metoxietoxi)fenil]acrilato de etilo (1.00 g) en tetrahidrofurano (5 ml) y etanol (5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4.5 ml), y la mezcla se agitó a 60°C durante 30 min. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-3-[2-{[2-cloro-4-(trifluorometil)fenil]amino}-4-(2-metoxietoxi)fenil]acrílico (515 mg, rendimiento: 55%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:3.29 (3 H, s), 3.62 - 3.65 (2 H, m), 4.10 - 4.13 (2 H, m), 6.39 (1 H, t, J = 16.1

Hz), 6.53 (1 H, d, J = 9.0 Hz), 6.80 (1 H, d, J = 2.4 Hz), 6.89 - 6.93 (1 H, m), 7.38 - 7.42 (1 H, m), 7.54 (1 H, t, J = 16.1 Hz), 7.74 (1 H, d, J = 2.1 Hz), 7.86 (1 H, d, J = 9.0 Hz), 8.18 (1 H, s), 12.19 (1 H, s).

Ejemplo de referencia 195

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (1.10 g) en N,N-dimetilformamida (10 ml) se añadieron 2-cloro-5-nitro-3-picolina (1.03 g) y carbonato de potasio (1.14 g), y la mezcla se agitó a 80°C durante 2 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-{4-(2-metoxietoxi)-2-[(3-metil-5-nitropiridin-2-il)oxi]fenil}acrilato de etilo (1.63 g, rendimiento: 98%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.27 (3 H, t, J = 7.1 Hz), 2.52 (3 H, s), 3.44 (3 H, s), 3.73 - 3.76 (2 H, m), 4.12 - 4.15 (2 H, m), 4.18 (2 H, q, J = 7.1 Hz), 6.32 (1 H, d, J = 16.2 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.90 (1 H, dd, J = 8.7, 2.4 Hz), 7.63 (1 H, d, J = 8.7 Hz), 7.64 (1 H, d, J = 16.2 Hz), 8.35 (1 H, d, J = 1.8 Hz), 8.81 (1 H, d, J = 1.8 Hz).

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Ejemplo de referencia 196

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (1.05 g) en N,N-dimetilformamida (10 ml) se añadieron 3-cloro-6-(trifluorometil)piridazina (1.48 g) y carbonato de potasio (1.53 g), y la mezcla se agitó a 80°C durante 3 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-metanol (49:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-(4-(2-metoxietoxi)-2-{[6-(trifluorometil)piridazin-3-il]oxi}fenil)acrilato de etilo (2.14 g, rendimiento: 90%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.27 (3 H, t, J = 7.1 Hz), 3.43 (3 H, s), 3.73 - 3.75 (2 H, m), 4.11 - 4.14 (2 H, m), 4.19 (2 H, q, J = 7.1 Hz), 6.35 (1 H, d, J = 16.2 Hz), 6.75 (1 H, d, J = 2.7 Hz), 6.91 (1 H, dd, J = 8.7, 2.7 Hz), 7.40 (1 H, d, J = 9.0 Hz), 7.64 (1 H, d, J = 8.7 Hz), 7.70 (1 H, d, J = 16.2 Hz), 7.84 (1 H, d, J = 9.0 Hz).

Ejemplo de referencia 197

A una solución de 2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benzaldehído (500 mg) en ácido acético (8 ml) se añadieron ácido metilmalónico (859 mg) y pirrolidina (827

mg), y la mezcla se agitó a 100°C durante 24 h. Se añadieron ácido clorhídrico 1 N (1 ml) y agua (10 ml) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 20 min. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar ácido (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-2-metilacrílico (455 mg, rendimiento: 78%) en forma de cristales incoloros. Punto de fusión 126.0-127.0°C.

Ejemplo de referencia 198

A una solución de 2-fosfonobutirato de trietilo (0.83 g) en tetrahidrofurano (10 ml) se añadió hidruro de sodio (60% en aceite, 145 mg) a 0°C, y la mezcla se agitó a 0°C durante 15 min. A esta mezcla de reacción se añadió una solución de 2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benzaldehído (1.02 g) en tetrahidrofurano (10 ml) a 0°C, y la mezcla se calentó hasta temperatura ambiente y se agitó durante 3 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en

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columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar (2E)-2-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benciliden]butanoato de etilo (922 mg, rendimiento: 70%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.08 (3 H, t, J = 7.2 Hz), 1.26 (3 H, t, J = 7.2 Hz), 2.45 (2 H, q, J = 7.2 Hz), 3.44 (3 H, s), 3.73 - 3.76 (2 H, m), 4.11 - 4.14 (2 H, m), 4.18 (2 H, q, J = 7.2 Hz), 6.74 (1 H, d, J = 3.0 Hz), 6.86 (1 H, dd, J = 9.0, 3.0 Hz), 7.34 (1 H, d, J = 9.0 Hz), 7.48 (1 H, s), 7.75 (1 H, d, J = 2.1 Hz), 7.91 (1 H, d, J = 2.1 Hz).

Ejemplo de referencia 199

A una solución mixta de (2E)-2-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benciliden]butanoato de etilo (908 mg) en tetrahidrofurano (5 ml) y etanol (5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (6 ml), y la mezcla se agitó a 60°C durante 6 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-2-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benciliden]butanoico (772 mg, rendimiento: 91%) en forma de cristales incoloros. Punto de fusión 139.0-139.9°C.

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Ejemplo de referencia 200

A una solución de 4-yodo-3-nitrofenol (5.33 g) en acetona (60 ml) se añadieron éter 2-bromoetilmetílico (11.1 g), yoduro de sodio (3.65 g) y carbonato de potasio (6.98 g), y la mezcla se calentó a reflujo durante 20 h. La mezcla de reacción se concentró, se vertió agua en el residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar 1-yodo-4-(2-metoxietoxi)-2-nitrobenceno (5.59 g, rendimiento: 86%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:3.44 (3 H, s), 3.76 (2 H, t, J = 4.5 Hz), 4.15 (2 H, t, J = 4.5 Hz), 6.90 (1 H, dd, J = 9.0, 2.7 Hz), 7.46 (1 H, d, J = 2.7 Hz), 7.87 (1 H, d, J = 9.0 Hz).

Ejemplo de referencia 201

A una solución de 1-yodo-4-(2-metoxietoxi)-2-nitrobenceno (5.59 g) en acetonitrilo (50 ml) se añadieron acrilato de etilo (2.62 g), trietilamina (3.62 g) y acetato de paladio (116 mg), y la mezcla se calentó a reflujo durante 5 h. Tras enfriar, la mezcla de reacción se concentró, se vertió agua en el residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con

salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-[4-(2-metoxietoxi)-2-nitrofenil]acrilato de etilo (4.94 g, rendimiento: 96%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.33 (3 H, t, J = 7.2 Hz), 3.46 (3 H, s), 3.78 (2 H, t, J = 4.5 Hz), 4.21 (2 H, t, J = 4.5 Hz), 4.27 (2 H, q, J = 7.2 Hz), 6.30 (1 H, d, J = 15.9 Hz), 7.21 (1 H, dd, J = 8.7, 2.7 Hz), 7.53 (1 H, d, J = 2.7 Hz), 7.57 (1 H, d, J = 8.7 Hz), 8.03 (1 H, d, J = 15.9 Hz).

Ejemplo de referencia 202

A una mezcla de agua (60 ml) y cinc (7.56 g) se añadió una solución de (2E)-3-[4-(2-metoxietoxi)-2-nitrofenil]acrilato de etilo (6.83 g) en ácido acético (60 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró, el residuo obtenido se alcalinizó con una solución acuosa 1 N de hidróxido de sodio, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-[2-amino-4-(2-metoxietoxi)fenil]acrilato de etilo (5.03 g, rendimiento: 82%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.32 (3 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.73 (2 H, t, J = 4.8 Hz), 3.95 (2 H, s), 4.09 (2 H, t, J = 4.8 Hz), 4.24 (2 H, q, J = 7.2 Hz), 6.20 - 6.25 (2 H, m), 6.36 (1 H, m), 7.33 (1 H, d, J = 8.7 Hz), 7.74 (1 H, d, J = 15.6 Hz).

Ejemplo de referencia 203

A una solución de (2E)-3-[2-amino-4-(2-metoxietoxi)fenil]acrilato de etilo (640 mg) en tetrahidrofurano (10 ml) se añadieron 2,4-cloruro de diclorobenzoilo (685 mg) y trietilamina (490 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró, se añadió agua al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con una solución acuosa de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. Los cristales crudos obtenidos se recristalizaron en etanol-hexano para dar (2E)-3-[2-[(2,4-diclorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrilato de etilo (812 mg, rendimiento: 77%) en forma de cristales incoloros. Punto de fusión 170.1-170.5°C.

Ejemplo de referencia 204

A una solución mixta de (2E)-3-[2-[(2,4-diclorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrilato de etilo (472 mg) en tetrahidrofurano (8 ml) y etanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (2.5 ml), y la mezcla se agitó a 60°C durante 2 h. Tras enfriar, la mezcla de

reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. Los cristales crudos obtenidos se recristalizaron en metanol-éter diisopropílico para dar ácido (2E)-3-[2-[(2,4-diclorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrílico (422 mg, rendimiento: 96%) en forma de cristales incoloros. Punto de fusión 242.8-244.8°C.

Ejemplo de referencia 205

A una solución de 2-hidroxi-4-(metoximetoxi)benzaldehído (7.04 g) en N,N-dimetilformamida (50 ml) se añadió hidruro de sodio (60% en aceite, 1.88 g), y la mezcla se agitó a temperatura ambiente durante 30 min. 2.3,5-Se añadieron tricloropiridina (7.40 g) a la mezcla de reacción, y la mezcla se agitó a 110°C durante 14 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5, v/v) para dar 2-[(3,5-dicloropiridin-2-il)oxi]-4-(metoximetoxi)benzaldehído (5.33 g, rendimiento: 42%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 3.48 (3 H, s), 5.23 (2 H,

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s), 6.85 (1 H, d, J = 2.4 Hz), 7.03 (1 H, dd, J = 9.0, 2.4 Hz), 7.82 (1 H, d, J = 2.4 Hz), 7.92 (1 H, d, J = 9.0 Hz), 7.95 (1 H, d, J = 2.4 Hz), 10.05 (1 H, s).

Ejemplo de referencia 206

A una solución de 2-[(3,5-dicloropiridin-2-il)oxi]-4-(metoximetoxi)benzaldehído (4.07 g) en acetona (25 ml) se añadió ácido clorhídrico 1 N (25 ml), y la mezcla se calentó a reflujo durante 2 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con una solución acuosa 1 N de hidróxido de sodio. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar 2-[(3,5-dicloropiridin-2-il)oxi]-4-hidroxibenzaldehído en forma de cristales incoloros (3.60 g, rendimiento: 99%).

^{1}H-RMN (300 MHz, DMSO-d_6) δ: 6.63 (1 H, d, J = 2.4 Hz), 6.85 (1 H, dd, J = 8.4, 2.1 Hz), 7.78 (1 H, d, J = 8.4 Hz), 8.13 (1 H, d, J = 2.4 Hz), 8.37 (1 H, d, J = 2.4 Hz), 9.81 (1 H, s), 10.95 (1 H, s).

Ejemplo de referencia 207

A una solución de 2-[(3,5-dicloropiridin-2-il)oxi]-4-hidroxibenzaldehído (3.60 g) en N,N-dimetilformamida (25 ml) se añadieron 1-bromo-3-metoxipropano (2.89 g), yoduro de sodio

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(2.85 g) y carbonato de potasio (3.48 g), y la mezcla se agitó a 80°C durante 2 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v) para dar 2-[(3,5-dicloropiridin-2-il)oxi]-4-(3-metoxipropoxi)benzaldehído (3.94 g, rendimiento: 87%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:2.01 - 2.10 (2 H, m), 3.34 (3 H, s), 3.53 (2 H, t, J = 6.0 Hz), 4.11 (2 H, t, J = 6.0 Hz), 6.68 (1 H, d, J = 2.1 Hz), 6.89 (1 H, dd, J = 8.7, 2.1 Hz), 7.82 (1 H, d, J = 2.4 Hz), 7.90 (1 H, d, J = 8.7 Hz), 7.95 (1 H, d, J = 2.4 Hz), 10.03 (1 H, s).

Ejemplo de referencia 208

A una solución de 2-[(3,5-dicloropiridin-2-il)oxi]-4-(3-metoxipropoxi)benzaldehído (745 mg) en ácido acético (12 ml) se añadieron ácido metilmalónico (1.24 g) y pirrolidina (1.18 g), y la mezcla se agitó a 100°C durante 66 h. Tras enfriar, se añadieron ácido clorhídrico 1 N (2 ml) y agua (10 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v). Los

cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar ácido (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(3-metoxipropoxi)fenil]-2-metilacrílico (658 mg, rendimiento: 76%) en forma de cristales incoloros. Punto de fusión 128.4-129.5°C.

Ejemplo de referencia 209

A una solución de (2E)-3-[2-amino-4-(2-metoxietoxi)fenil]acrilato de etilo (615 mg) en tetrahidrofurano (15 ml) se añadieron cloruro de 2,4-difluorobenzoilo (490 mg) y trietilamina (480 mg), y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró, una solución acuosa de carbonato ácido de sodio se añadió al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con una solución acuosa de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$) y se concentró. Los cristales crudos obtenidos se recristalizaron en tetrahidrofurano-hexano para dar (2E)-3-[2-[(2,4-difluorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrilato de etilo (718 mg, rendimiento: 76%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.33 (3 H, t, J = 7.2 Hz), 3.45 (3 H, s), 3.75 - 3.78 (2 H, m), 4.17 - 4.21 (2 H, m), 4.26 (2 H, q, J = 7.2 Hz), 6.34 (1 H, d, J = 15.6 Hz), 6.84 (1 H, dd, J = 8.7, 2.7 Hz), 6.93 - 7.11 (2 H, m), 7.54 (1 H, d, J = 8.7 Hz), 7.72 (1 H, d, J = 2.7 Hz), 7.85 (1 H, d, J = 15.6

Hz), 8.20 - 8.25 (1 H, m), 8.44 - 8.49 (1 H, m).

Ejemplo de referencia 210

A una solución mixta de (2E)-3-[2-[(2,4-difluorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrilato de etilo (572 mg) en tetrahidrofurano (6 ml) y etanol (6 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (3 ml), y la mezcla se agitó a 60°C durante 2 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en tetrahidrofurano-hexano para dar ácido (2E)-3-[2-[(2,4-difluorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrílico (460 mg, rendimiento: 86%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:3.31 (3 H, s), 3.65 - 3.68 (2 H, m), 4.12 - 4.15 (2 H, m), 6.37 (1 H, d, J = 15.6 Hz), 6.91 (1 H, dd, J = 8.7, 2.4 Hz), 7.08 (1 H, s), 7.22 - 7.30 (1 H, m), 7.41 - 7.49 (1 H, m), 7.72 (1 H, d, J = 15.6 Hz), 7.79 - 7.82 (2 H, m), 10.27 (1 H, s), 12.22 (1 H, s).

Ejemplo de referencia 211

A una mezcla de agua (5 ml) y cinc (379 mg) se añadió una solución de (2E)-3-{4-(2-metoxietoxi)-2-[(3-metil-5-nitropiridin-2-il)oxi]fenil}acrilato de etilo (455 mg) en ácido acético (5 ml), y la mezcla se agitó a temperatura

ambiente durante 2 h. La mezcla de reacción se concentró, el residuo obtenido se alcalinizó con una solución acuosa 8 N de hidróxido de sodio, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-[2-[(5-amino-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (307 mg, rendimiento: 73%) en forma de cristales marrones.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.2 Hz), 2.23 (3 H, s), 3.41 (3 H, s), 3.51 (2 H, s), 3.67 - 3.71 (2 H, m), 4.03 - 4.07 (2 H, m), 4.21 (2 H, q, J = 7.2 Hz), 6.38 (1 H, s), 6.41 (1 H, d, J = 15.9 Hz), 6.67 (1 H, dd, J = 8.7, 2.4 Hz), 6.96 (1 H, d, J = 2.4 Hz), 7.52 - 7.55 (2 H, m), 7.93 (1 H, d, J = 15.9 Hz).

Ejemplo de referencia 212

A una solución de (2E)-3-[2-[(5-amino-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (300 mg) en tetrahidrofurano (10 ml) se añadió dicarbonato de di-ter-butilo (880 mg), y la mezcla se agitó a 60°C durante 11 h. La mezcla de reacción se concentró, el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar (2E)-3-[2-({5-[(ter-butoxicarbonil)amino]-3-

metilpiridin-2-il}oxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (351 mg, rendimiento: 92%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.29 (3 H, t, J = 7.2 Hz), 1.52 (9 H, s), 2.35 (3 H, s), 3.41 (3 H, s), 3.69 - 3.72 (2 H, m), 4.05 - 4.08 (2 H, m), 4.20 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 15.9 Hz), 6.34 - 6.40 (1 H, m), 6.49 (1 H, d, J = 2.7 Hz), 6.74 (1 H, dd, J = 8.7, 2.7 Hz), 7.57 (1 H, d, J = 8.7 Hz), 7.78 - 7.79 (1 H, m), 7.85 (1 H, d, J = 15.9 Hz), 7.93 (1H, s).

Ejemplo de referencia 213

A una solución mixta de (2E)-3-[2-({5-[(ter-butoxicarbonil)amino]-3-metilpiridin-2-il}oxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (351 mg) en tetrahidrofurano (3 ml) y etanol (3 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (1.5 ml), y la mezcla se agitó a 60°C durante 1 hora. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-3-[2-({5-[(ter-butoxicarbonil)amino]-3-metilpiridin-2-il}oxi)-4-(2-metoxietoxi)fenil]acrílico (327 mg, rendimiento: 99%) en forma

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de cristales incoloros. Punto de fusión 159.0-160.0°C.

Ejemplo de referencia 214

A una mezcla de etilenglicol (34 ml) y piridina (34 ml) se añadió gota a gota cloro(triisopropil)silano (10.7 ml) a temperatura ambiente durante 20 min, y la mezcla se agitó durante 12 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa acuosa se lavó con acetato de etilo, y la capa orgánica obtenida se lavó con agua y salmuera saturada, se secó y se concentró. El residuo obtenido se sometió a cromatografía en columna, y se eluyó con acetato de etilo-hexano (1:20 - 1:5, v/v) para dar una 2-[(triisopropilsilil)oxi]etanol (10.48 g, rendimiento: 96%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.99 - 1.17 (21 H, m), 2.17 (1 H, t, J = 6.2 Hz), 3.58 - 3.71 (2 H, m), 3.74 - 3.85 (2 H, m).

Ejemplo de referencia 215

A una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (1.50 g), 2-[(triisopropilsilil)oxi]etanol (1.01 g), tributilfosfina (2.41 ml) y tetrahidrofurano (50 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.95 g) a temperatura ambiente, y la mezcla se agitó durante 16 h. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró,

y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:20 - 1:3, v/v) para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)acrilato de etilo en forma de un aceite de color amarillo pálido (2.02 g, rendimiento: 89%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.97 - 1.15 (21 H, m), 1.28 (3 H, t, J = 7.1 Hz), 3.98 - 4.12 (4 H, m), 4.20 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 16.2 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 8.8, 2.5 Hz), 7.62 (1 H, d, J = 8.7 Hz), 7.68 (1 H, d, J = 16.2 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 216

Una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)acrilato de etilo (1.22 g), una solución acuosa 1 N de hidróxido de sodio (4.14 ml), tetrahidrofurano (3.2 ml) y etanol (3.2 ml) se agitó a 50°C durante 2 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (4.14 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se lavó con éter dietílico-hexano, y el material insoluble se filtró. El filtrado se concentró. El residuo se sometió a

cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 2:1, v/v) para dar ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)acrílico (0.99 g, rendimiento: 85%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.95 - 1.17 (21 H, m), 3.88 - 4.20 (4 H, m), 6.36 (1 H, d, J = 16.0 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.90 (1 H, dd, J = 8.7, 2.5 Hz), 7.64 (1 H, d, J = 8.9 Hz), 7.76 (1 H, d, J = 16.0 Hz), 8.02 (1 H, dd, J = 2.3, 0.4 Hz), 8.25 (1 H, dd, J = 2.3, 0.9 Hz).

Ejemplo de referencia 217

A una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (3.00 g), 1.3-dietoxipropan-2-ol (1.38 g), tributilfosfina (4.81 ml) y tetrahidrofurano (100 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (3.91 g) a temperatura ambiente, y la mezcla se agitó durante 16 h. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:20 - 1:3, v/v) para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}acrilato de etilo en forma de un aceite incoloro (1.97 g, rendimiento: 49%). La cristalización

en éter dietílico-hexano dio un polvo blanco. Punto de fusión 66-67.5°C.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.17 (6 H, t, J = 7.0 Hz), 1.28 (3 H, t, J = 7.2 Hz), 3.52 (4 H, qd, J = 7.0, 0.9 Hz), 3.59 - 3.74 (4 H, m), 4.20 (2 H, q, J = 7.0 Hz), 4.41 - 4.59 (1 H, m), 6.37 (1 H, d, J = 16.0 Hz), 6.79 (1 H, d, J = 2.5 Hz), 6.95 (1 H, dd, J = 8.8, 2.5 Hz), 7.61 (1 H, d, J = 8.7 Hz), 7.70 (1 H, d, J = 16.2 Hz), 8.01 (1 H, d, J = 2.3 Hz), 8.24 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo de referencia 218

Una mezcla de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}acrilato de etilo (1.96 g), una solución acuosa 1 N de hidróxido de sodio (7.4 ml), tetrahidrofurano (3.5 ml) y etanol (3.5 ml) se agitó a 50°C durante 2 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (7.4 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se recristalizó en acetato de etilo-hexano. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:25 - 1:5 - 1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-

(etoximetil)etoxi]fenil}acrílico (407 mg, rendimiento: 23%) en forma de cristales incoloros. Punto de fusión 62-63°C.

Ejemplo de referencia 219

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (3.00 g) en N,N-dimetilformamida (10 ml) se añadieron carbonato de potasio (2.14 g), yoduro de sodio (1.74 g) y 2-(2-bromoetil)-1,3-dioxolano (1.36 ml) a temperatura ambiente, y la mezcla se agitó a 80°C durante 12 h. Tras enfriar, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:1, v/v). Los cristales crudos obtenidos se recristalizaron en éter dietílico-hexano para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(1,3-dioxolan-2-il)etoxi]fenil}acrilato de etilo (2.75 g, rendimiento: 73%) en forma de un polvo blanco. Punto de fusión 102-103°C.

Ejemplo de referencia 220

Una mezcla de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(1,3-dioxolan-2-il)etoxi]fenil}acrilato de etilo (2.71 g), una solución acuosa 1 N de hidróxido de sodio (11.1 ml), tetrahidrofurano (11 ml) y etanol (11 ml) se agitó a 50°C durante 2 h. La mezcla de

reacción se concentró, se añadió ácido clorhídrico 1 N (11.1 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(1,3-dioxolan-2-il)etoxi]fenil}acrílico (2.11 g, rendimiento: 83%) en forma de cristales incoloros. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:10 - 2:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar cristales incoloros. Punto de fusión 157-158.5°C.

Ejemplo de referencia 221

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (4.02 g) en N,N-dimetilformamida (25 ml) se añadieron carbonato de potasio (2.87 g), yoduro de sodio (3.12 g) y 2-(bromometil)tetrahidrofurano (2.34 ml) a temperatura ambiente, y la mezcla se agitó a 80°C durante 16 h. Tras enfriar, se añadió agua a la mezcla de reacción, y se extrajo con acetato de etilo-hexano (1:1, v/v). La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:3, v/v). Los cristales crudos obtenidos se recristalizaron en

éter diisopropílico-hexano para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]acrilato de etilo (1.85 g, rendimiento: 38%) en forma de un polvo blanco. Punto de fusión 84-86°C.

Ejemplo de referencia 222

Una mezcla de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]acrilato de etilo (1.75 g), una solución acuosa 1 N de hidróxido de sodio (7.4 ml), tetrahidrofurano (3.5 ml) y etanol (3.5 ml) se agitó a 50°C durante 2 h. Se añadió ácido clorhídrico 1 N (7.4 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en éter dietílico-hexano para dar ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]acrílico (0.79 g, rendimiento: 48%) en forma de cristales blancos. Punto de fusión 106-109°C.

Ejemplo de referencia 223

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (4.02 g) en N,N-dimetilformamida (25 ml) se añadieron carbonato de potasio (2.87 g), yoduro de sodio (3.12 g) y 2-cloropirimidina (2.38 g) a temperatura ambiente, y la mezcla se agitó a 80°C durante 12 h. Tras enfriar, se añadió agua a la

mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna con NH-gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:2, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(pirimidin-2-iloxi)fenil]acrilato de etilo (2.50 g, rendimiento: 54%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.30 (3 H, t, J = 7.2 Hz), 4.22 (2 H, q, J = 7.2 Hz), 6.47 (1 H, d, J = 16.2 Hz), 7.04 - 7.13 (2 H, m), 7.20 (1 H, dd, J = 8.7, 2.5 Hz), 7.75 (1 H, d, J = 3.6 Hz), 7.79 (1 H, d, J = 11.1 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz), 8.59 (2 H, d, J = 4.9 Hz).

Ejemplo de referencia 224

Una mezcla de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(pirimidin-2-iloxi)fenil]acrilato de etilo (2.38 g), una solución acuosa 1 N de hidróxido de sodio (11 ml), tetrahidrofurano (12 ml) y etanol (12 ml) se agitó a 50°C durante 2 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (11 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía

en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:25 - 1:5 - 1:1, v/v) para dar ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(pirimidin-2-iloxi)fenil]acrílico (1.26 g, rendimiento: 54%) en forma de un polvo amorfo.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:6.49 (1 H, d, J = 16.0 Hz), 7.03 - 7.14 (2 H, m), 7.22 (1 H, dd, J = 8.6, 2.4 Hz), 7.78 (1 H, d, J = 8.7 Hz), 7.86 (1 H, d, J = 16.2 Hz), 8.02 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz), 8.60 (2 H, d, J = 4.9 Hz).

Ejemplo de referencia 225

A una mezcla de 3-isopropoxi-1H-pirazol-5-carboxilato de metilo (1.55 g), carbonato de potasio (1.75 g) y N,N-dimetilformamida (15 ml) se añadió 3-cloro-2-(clorometil)-5-(trifluorometil)piridina (1.94 g) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 h. Se vertió agua en la mezcla de reacción, y la mezcla se dividió en agua y acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:49 - 1:9, v/v) para dar 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-carboxilato de metilo (1.63 g, rendimiento: 51%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.3 Hz),

3.80 (3 H, s), 4.63 - 4.76 (1 H, m), 5.92 (2 H, s), 6.30 (1 H, s), 7.87 - 7.92 (1 H, m), 8.59 - 8.63 (1 H, m).

Ejemplo de referencia 226

Una mezcla de 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-carboxilato de metilo (1.92 g), una solución acuosa 1 N de hidróxido de sodio (20 ml), tetrahidrofurano (20 ml) y metanol (10 ml) se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N (100 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar ácido 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-carboxílico (1.63 g, rendimiento: 88%) en forma de cristales incoloros. Punto de fusión 124-125°C.

Ejemplo de referencia 227

Una mezcla de clorhidrato de N,O-dimetilhidroxilamina (515 mg), trietilamina (534 mg) y N,N-dimetilformamida (30 ml) se agitó a temperatura ambiente durante 30 min, se añadieron ácido 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-carboxílico (1.60 g), clorhidrato de 1-etil-3-(3'-dimetilaminopropil)carbodiimida (1.01 g) y 1-hidroxibenzotriazol monohidratado (809 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de

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reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:4, v/v) para dar 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-N-metoxi-N-metil-1H-pirazol-5-carboxamida (1.37 g, rendimiento: 77%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.33 (6 H, d, J = 6.0 Hz), 3.28 (3 H, s), 3.72 (3 H, s), 4.67 - 4.80 (1 H, m), 5.92 (2 H, s), 6.30 (1 H, s), 7.86 - 7.90 (1 H, m), 8.53 - 8.57 (1 H, m).

Ejemplo de referencia 228

A una solución de 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-N-metoxi-N-metil-1H-pirazol-5-carboxamida (1.36 g) en tetrahidrofurano (25 ml) se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (3.4 ml) a 0°C, y la mezcla se agitó durante 2 h. Además, a la mezcla de reacción se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (1.5 ml) a 0°C, y la mezcla se agitó durante 30 min. Se añadió metanol para neutralizar la reacción. La mezcla de reacción se vertió en una solución acuosa al 10% de sal de Rochelle, y la mezcla se agitó y se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo

se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:4, v/v) para dar 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-carbaldehído (640 mg, rendimiento: 55%) en forma de un aceite marrón.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.34 (6 H, d, J = 6.0 Hz), 4.68 - 4.81 (1 H, m), 5.87 (2 H, s), 6.35 (1 H, s), 7.88 - 7.92 (1 H, m), 8.56 - 8.61 (1 H, m), 9.74 (1 H, s).

Ejemplo de referencia 229

Bajo enfriamiento con hielo, a una solución de dietilfosfonoacetato de etilo (619 mg) en N,N-dimetilformamida (6.0 ml) se añadió hidruro de sodio (60% en aceite, 96 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo otra vez, se añadió una solución de 1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-carbaldehído (640 mg) en tetrahidrofurano (6.0 ml), y la mezcla se agitó a 0°C durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar (2E)-3-(1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-il)acrilato de etilo (640 mg, rendimiento: 83%) en forma de un aceite de color amarillo pálido.

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^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.31 (3 H, t, J = 7.2 Hz), 1.31 (6 H, d, J = 6.0 Hz), 4.23 (2 H, d, J = 7.2 Hz), 4.61 - 4.74 (1 H, m), 5.56 (2 H, s), 6.02 (1 H, s), 6.32 (1 H, d, J = 15.6 Hz), 7.48 (1 H, d, J = 15.6 Hz), 7.91 - 7.95 (1 H, m), 8.65 - 8.70 (1 H, m).

Ejemplo de referencia 23

Una mezcla de (2E)-3-(1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-il)acrilato de metilo (640 mg), una solución acuosa 1 N de hidróxido de sodio (3.0 ml), tetrahidrofurano (6.0 ml) y etanol (6.0 ml) se agitó a 50°C durante 1 hora, se añadió ácido clorhídrico 1 N (20 ml), y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. Los cristales crudos obtenidos se recristalizaron en hexano-acetato de etilo para dar ácido (2E)-3-(1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-il)acrílico (460 mg, rendimiento: 77%) en forma de cristales incoloros. Punto de fusión 130-132°C.

Ejemplo de referencia 231

A una solución de alcohol bencílico (3.06 g) en diclorometano (150 ml) se añadió clorosulfonilisocianato (2.55 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (8.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 4-

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metilciclohexilamina (18.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio {[(4-metilciclohexil)amino]sulfonil}carbamato de bencilo (6.64 g, rendimiento: 72%) en forma de cristales blancos. La recristalización en acetato de etilo-éter diisopropílico dio cristales en pluma blancos. Punto de fusión 153-155°C.

Ejemplo de referencia 232

A una solución de {[(4-metilciclohexil)amino]sulfonil}carbamato de bencilo (6.34 g) en tetrahidrofurano (40 ml) y etanol (40 ml) se añadió paladio sobre carbón al 10% (3.41 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró, y el filtrado se concentró. La recristalización del residuo obtenido en acetato de etilo-hexano dio N-(4-metilciclohexil)sulfamida (3.19 g, rendimiento: 86%) en forma de cristales de mica blancos. Punto de fusión 109-110°C.

Ejemplo de referencia 233

A una solución de alcohol bencílico (3.02 g) en

diclorometano (150 ml) se añadió clorosulfonilisocianato (2.55 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (8.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-(2-tienil)etilamina (5.0 g), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se lavó con éter diisopropílico. La recristalización en acetato de etilo-hexano dio ({[2-(2-tienil)etil]amino}sulfonil)carbamato de bencilo (8.29 g, rendimiento: 87%) en forma de cristales blancos. La recristalización en acetato de etilo-éter diisopropílico dio cristales blancos. Punto de fusión 129-131°C.

Ejemplo de referencia 234

Una solución de ({[2-(2-tienil)etil]amino}sulfonil)carbamato de bencilo (6.34 g) en ácido bromhídrico-ácido acético al 25% p/p (25 ml) y ácido acético (10 ml) se agitó a temperatura ambiente durante 1 hora, y luego a 45°C durante 30 min. La mezcla de reacción se vertió en una solución acuosa saturada de carbonato ácido de sodio enfriada con hielo, y se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se filtró,

se secó ($MgSO_4$), se filtró y se concentró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (15:85 - 1:1, v/v) para dar un sólido marrón pálido. La recristalización en acetato de etilo-hexano dio N-[2-(2-tienil)etil]sulfamida (3.21 g, rendimiento: 66%) en forma de un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio cristales blancos.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.13 (2 H, t, J = 6.6 Hz), 3.43 (2 H, q, J = 6.5 Hz), 4.36 - 4.60 (3 H, m), 6.89 (1 H, dd, J = 3.5, 1.0 Hz), 6.96 (1 H, dd, J = 5.2, 3.5 Hz), 7.19 (1 H, dd, J = 5.2, 1.2 Hz).

Ejemplo de referencia 235

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrilato de etilo (3.00 g) en tetrahidrofurano (30 ml) se añadió paladio-carbón al 5% (1.51 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar un aceite incoloro.

A una solución del aceite obtenido en tetrahidrofurano (5 ml) y etanol (5 ml) se añadió una solución

acuosa 1 N de hidróxido de sodio (15 ml), y la mezcla se agitó a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadieron ácido clorhídrico 1 N (15 ml) y una pequeña cantidad de tolueno a la mezcla de reacción, y la mezcla se concentró. El residuo obtenido se disolvió en acetato de etilo, y la solución se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilpropanoico (1.25 g, rendimiento: 52%) en forma de cristales blancos. Punto de fusión 129.5-131.0°C.

Ejemplo de referencia 236

A una solución de 2-(benciloxi)-4-(2-metoxietoxi)benzaldehído (11.92 g) en tetrahidrofurano (80 ml) se añadieron metoxiacetato de metilo (6.16 g) y t-butóxido de potasio (6.81 g), y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:2, v/v) para dar un aceite amarillo.

A una solución del aceite obtenido en metanol (100 ml) se añadió paladio sobre carbón al 10% (5.01 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 5 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55, v/v) para dar 3-[2-hidroxi-4-(2-metoxietoxi)fenil]-2-metoxipropanoato de metilo (3.45 g, rendimiento: 29%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.91 - 3.11 (2 H, m), 3.44 (3 H, s), 3.49 (3 H, s), 3.70 - 3.77 (5 H, m), 4.01 - 4.12 (3 H, m), 6.43 (1 H, dd, J = 8.3, 2.6 Hz), 6.51 (1 H, d, J = 2.6 Hz), 6.91 (1 H, d, J = 8.3 Hz), 7.69 (1 H, s).

Ejemplo de referencia 237

A una solución de 3-[2-hidroxi-4-(2-metoxietoxi)fenil]-2-metoxipropanoato de metilo (1.84 g) en N,N-dimetilformamida (30 ml) se añadió bajo enfriamiento con hielo hidruro de sodio (60% en aceite, 311 mg), y la mezcla se agitó posteriormente durante 30 min. Luego se añadió 2.3-dicloro-5-(trifluorometil)piridina (1.0 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a

cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metoxipropanoato de metilo (2.26 g, rendimiento: 75%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.76 - 2.94 (2 H, m), 3.28 (3 H, s), 3.44 (3 H, s), 3.67 (3 H, s), 3.71 - 3.76 (2 H, m), 3.95 (1 H, dd, J = 7.9, 5.5 Hz), 4.07 - 4.12 (2 H, m), 6.69 - 6.72 (1 H, m), 6.82 (1 H, dd, J = 8.6, 2.5 Hz), 7.22 - 7.30 (1 H, m), 7.99 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.3, 0.9 Hz).

Ejemplo de referencia 238

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metoxipropanoato de metilo (2.26 g) en tetrahidrofurano (5 ml) y metanol (5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (15 ml), y la mezcla se agitó a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadieron ácido clorhídrico 1 N (15 ml) y una pequeña cantidad de tolueno a la mezcla de reacción, y la mezcla se concentró. El residuo obtenido se disolvió en acetato de etilo, y la mezcla se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 solo a 65:35, v/v) para dar un

sólido blanco. La recristalización en acetato de etilo-hexano dio ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metoxipropanoico (1.19 g, rendimiento: 54%) en forma de cristales blancos. Punto de fusión 93-96°C.

Ejemplo de referencia 239

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrilato de etilo (2.37 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (15 ml), y la mezcla se agitó a 50°C durante 4 h. Una solución acuosa 1 N de hidróxido de sodio (15 ml) se añadió a la mezcla de reacción, y la mezcla se siguió agitando durante 3 h. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (30 ml) a la mezcla de reacción, y la mezcla se diluyó con tolueno y se concentró. El residuo se disolvió en acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar un sólido blanco. El sólido obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (35:65 - 7:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (741 mg, rendimiento:

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33%) en forma de agujas blancas. Punto de fusión 122.0-122.5°C.

Ejemplo de referencia 240

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (9.92 g) en tetrahidrofurano (60 ml) y éter dietílico (240 ml) se añadieron piridina (0.50 ml) y cloruro de tionilo (4.5 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:9, v/v) para dar una 3-cloro-2-[2-(clorometil)-5-(2-metoxietoxi)fenoxi]-5-(trifluorometil)piridina (8.06 g, rendimiento: 77%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 108-111°C.

Ejemplo de referencia 241

A una solución de alcohol bencílico (3.06 g) en diclorometano (150 ml) se añadió clorosulfonilisocianato (2.55 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (8.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se añadió 1-pentilamina

(16.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio [(pentilamino)sulfonil]carbamato de bencilo (8.18 g, rendimiento: 96%) en forma de cristales blancos. Punto de fusión 142.5-143.0°C.

Ejemplo de referencia 242

A una solución de [(pentilamino)sulfonil]carbamato de bencilo (5.83 g) en tetrahidrofurano (50 ml) y etanol (50 ml) se añadió paladio sobre carbón al 10% (3.11 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se recristalizó en acetato de etilo-éter diisopropílico para dar N-pentilsulfamida (3.15 g, rendimiento: 98%) en forma de cristales de mica blancos. Punto de fusión 60-63°C.

Ejemplo de referencia 243

A una solución de difenilfosfonoacetato de etilo (1.08 g) en tetrahidrofurano (50 ml) se añadió una solución metanólica al 40% de Tritón B (marca registrada) (1.60 ml) a -78°C, 15 min más tarde, se añadió una solución de 2-{[3-cloro-

5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)benzaldehído (1.15 g) en tetrahidrofurano (15 ml) gota a gota, y la mezcla se agitó durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 35:65, v/v) para dar (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilato de etilo (1.12 g, rendimiento: 82%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.23 (3 H, t, J = 7.1 Hz), 3.43 (3 H, s), 3.72 - 3.77 (2 H, m), 4.08 - 4.19 (4 H, m), 5.83 (1 H, d, J = 12.4 Hz), 6.70 (1 H, d, J = 2.2 Hz), 6.83 (1 H, d, J = 12.4 Hz), 6.83 - 6.89 (1 H, m), 7.78 (1 H, d, J = 8.8 Hz), 7.96 (1 H, d, J = 1.9 Hz), 8.24 (1 H, dd, J = 2.1, 1.0 Hz).

Ejemplo de referencia 244

A una solución de (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilato de etilo (1.12 g) en tetrahidrofurano (4 ml), etanol (4 ml) y agua (4 ml) se añadió hidróxido de litio monohidratado (256 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. Bajo

enfriamiento con hielo, también se agregó hidróxido de litio monohidratado (412 mg), y la mezcla se agitó durante 30 min. Se añadió ácido clorhídrico 1 N (16 ml) a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (780 g, rendimiento: 74%) en forma de cristales blancos. Punto de fusión 131.8-132.0°C.

Ejemplo de referencia 245

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.00 g) en tetrahidrofurano (100 ml) se añadieron tributilfosfina (5.40 ml), 2-{[ter-butil(difenil)silil]oxi}etanol (5.82 g) y 1.1'-(azodicarbonil)dipiperidina (4.97 g), y la mezcla se agitó durante la noche a 50°C. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrilato de etilo (7.51 g, rendimiento: 87%) en forma de un aceite blanco.

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^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.04 (9 H, s), 1.22 - 1.29 (3 H, m), 3.98 (2 H, t, J = 4.9 Hz), 4.06 - 4.15 (2 H, m), 4.15 - 4.27 (2 H, m), 6.36 (1 H, d, J = 16.0 Hz), 6.65 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.7, 2.4 Hz), 7.32 - 7.49 (6 H, m), 7.61 (1 H, d, J = 8.9 Hz), 7.65 - 7.78 (5 H, m), 8.01 (1 H, d, J = 2.3 Hz), 8.23 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplos de referencia 246, 247

A una solución de (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrilato de etilo (7.02 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (25 ml) a temperatura ambiente, y la mezcla se agitó durante 4 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar ácido (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrílico (789 mg rendimiento: 12%) (Ejemplo de referencia 246) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.04 (9 H, s), 3.98 (2 H, t, J = 5.2 Hz), 4.10 (2 H, t, J = 4.7 Hz), 6.37 (1 H, d, J =

16.0 Hz), 6.64 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.7, 1.7 Hz), 7.30 - 7.47 (6 H, m), 7.62 (1 H, d, J = 8.7 Hz), 7.68 (4 H, dd, J = 7.8, 1.6 Hz), 7.75 (1 H, d, J = 16.0 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.06 - 8.30 (1 H, m).

Luego se obtuvo un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxietoxi)fenil]acrílico monohidratado (132 mg, rendimiento: 3%) (Ejemplo de referencia 247) en forma de cristales blancos. Punto de fusión 153.0-153.2°C.

Ejemplo de referencia 248

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (2.60 g) en N,N-dimetilformamida (20 ml) se añadieron carbonato de potasio (2.20 g) y 4-fluoronitrobenceno (1.50 ml), y la mezcla se agitó durante la noche a temperatura ambiente, y luego a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar una (2E)-3-[4-(2-metoxietoxi)-2-(4-nitrofenoxi)fenil]acrilato de etilo (3.97 g,

cuant.) en forma de un sólido amarillo. La recristalización en acetato de etilo-hexano dio cristales de color amarillo pálido en forma de 0.3 hidrato. Punto de fusión 61-64°C.

Ejemplo de referencia 249

A una solución de (2E)-3-[4-(2-metoxietoxi)-2-(4-nitrofenoxi)fenil]acrilato de etilo (3.89 g) en etanol (50 ml) y tetrahidrofurano (10 ml) se añadió paladio sobre carbón al 10% (0.91 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. La mezcla de reacción se filtró y el filtrado se concentró para dar (2E)-3-[2-(4-aminofenoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (2.97 g, rendimiento: 84%) en forma de un aceite marrón pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.22 (3 H, t, J = 7.1 Hz), 2.56 - 2.72 (2 H, m), 2.94 (2 H, t, J = 7.7 Hz), 3.40 (3 H, s), 3.57 (2 H, s), 3.63 - 3.71 (2 H, m), 3.93 - 3.99 (2 H, m), 4.10 (2 H, q, J = 7.1 Hz), 6.31 (1 H, d, J = 2.5 Hz), 6.51 (1 H, dd, J = 8.5, 2.5 Hz), 6.61 - 6.71 (2 H, m), 6.74 - 6.88 (2 H, m), 7.09 (1 H, d, J = 8.2 Hz).

Ejemplo de referencia 250

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)-2-metilacrilato de etilo (4.61 g) en N,N-dimetilformamida (20 ml) se añadieron carbonato de potasio (3.12 g) y yoduro de isopropilo (2.0 ml), y la mezcla se agitó a 50°C durante 1

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hora. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrilato de etilo (3.46 g, rendimiento: 68%) en forma de cristales blancos. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 61.0-62.0°C.

Ejemplo de referencia 251

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrilato de etilo (3.46 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (20 ml), y la mezcla se agitó a 50°C durante 2 h. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (20 ml) se añadió a la mezcla de reacción, y la mezcla se concentró y se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 7:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano

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dio ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (2.02 g, rendimiento: 62%) en forma de cristales blancos. Punto de fusión 114.4-114.5°C.

Ejemplo de referencia 252

A una solución de alcohol bencílico (3.05 g) en diclorometano (60 ml) se añadió clorosulfonilisocianato (2.50 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (8.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-feniletilamina (8.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio {[(2-feniletil)amino]sulfonil}carbamato de bencilo (8.27 g, rendimiento: 88%) en forma de cristales blancos. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 120.0-121.0°C.

Ejemplo de referencia 253

A una solución de {[(2-feniletil)amino]sulfonil}carbamato de bencilo (7.97 g) en

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etanol (100 ml) se añadió paladio sobre carbón al 10% (7.51 g), y la mezcla se agitó durante la noche bajo una atmósfera de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró, y el filtrado se concentró. La recristalización del residuo obtenido en acetato de etilo-hexano dio N-(2-feniletil)sulfamida (4.45 g, rendimiento: 93%) en forma de cristales blancos. Punto de fusión 61.8-62.0°C.

Ejemplo de referencia 254

A una solución de alcohol bencílico (3.05 g) en diclorometano (60 ml) se añadió clorosulfonilisocianato (2.50 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (8.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 3-metoxipropilamina (8.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(3-metoxipropil)amino]sulfonil}carbamato de bencilo (1.14 g, rendimiento: 13%) en forma de cristales blancos. Punto de fusión 91-93°C.

Ejemplo de referencia 255

A una solución de {[(3-metoxipropil)amino]sulfonil}carbamato de bencilo (1.11 g) en

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etanol (5 ml) se añadió paladio sobre carbón al 10% (1.22 g), y la mezcla se agitó durante la noche bajo una atmósfera de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró y el filtrado se concentró para dar N-(3-metoxipropil)sulfamida (631 mg, cuant.) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.86 (2 H, tt, J = 5.9, 5.9 Hz), 3.26 (2 H, t, J = 6.2 Hz), 3.34 (3 H, s), 3.52 (2 H, t, J = 5.7 Hz), 4.69 (2 H, br. s.).

Ejemplo de referencia 256

A una solución de alcohol bencílico (3.05 g) en diclorometano (60 ml) se añadió clorosulfonilisocianato (2.50 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (8.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-isopropoxietilamina (8.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de bencilo (7.91 g, rendimiento: 89%) en forma de cristales blancos. Punto de fusión 88-89°C.

Ejemplo de referencia 257

A una solución de {[(2-isopropoxietil)amino]sulfonil}carbamato de bencilo (7.76 g) en etanol (50 ml) se añadió paladio sobre carbón al 10% (7.01 g), y la mezcla se agitó durante la noche bajo una atmósfera de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró y el filtrado se concentró para dar N-(2-isopropoxietil)sulfamida (4.44 g, rendimiento: 99%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.17 (6 H, d, J = 6.0 Hz), 3.24 - 3.37 (2 H, m), 3.49 - 3.72 (3 H, m), 4.30 - 5.00 (3 H, m).

Ejemplo de referencia 258

A una solución de alcohol bencílico (5.41 g) en acetonitrilo (500 ml) se añadió clorosulfonilisocianato (4.40 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (12.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se añadió 1-(tetrahidrofurano-2-il)metanamina (10.5 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización

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en acetato de etilo-hexano dio {[(tetrahidrofurano-2-ilmetil)amino]sulfonil}carbamato de bencilo (14.7 g, rendimiento: 94%) en forma de cristales blancos. Punto de fusión 96-97°C.

Ejemplo de referencia 259

A una solución de {[(tetrahidrofurano-2-ilmetil)amino]sulfonil}carbamato de bencilo (14.2 g) en etanol (200 ml) se añadió paladio sobre carbón al 10% (5.21 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 5 h. La mezcla de reacción se filtró y el filtrado se concentró para dar N-(tetrahidrofurano-2-ilmetil)sulfamida (8.35 g, cuant.) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 1.52 - 1.70 (1 H, m), 1.85 - 2.08 (3 H, m), 3.07 - 3.20 (1 H, m), 3.24 - 3.34 (1 H, m), 3.72 - 3.83 (1 H, m), 3.88 (1 H, ddd, J = 8.3, 6.7 Hz), 4.05 - 4.13 (1 H, m), 4.77 (3 H, br. s.).

Ejemplo de referencia 260

Una solución de 3-(metiltio)propan-1-ol (5.30 g), trietilamina (10.5 ml) y N,N,N',N'-tetrametil-1.6-hexanodiamina (0.86 g) en tolueno (50 ml) se enfrió en hielo, y cloruro de p-toluensulfonilo (14.3 g) en tolueno (50 ml) se añadió gota a gota bajo una atmósfera de nitrógeno. Después de completar la adición gota a gota, la mezcla se dejó calentar hasta temperatura ambiente y se agitó durante 3 h. Se añadió

agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó (Na_2SO_4) y se concentró a presión reducida. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar 4-metilbencensulfonato de 3-(metiltio)propilo (12.2 g, rendimiento: 94%) en forma de un aceite incoloro. MS m/z 261 (MH^+).

Ejemplo de referencia 261

A una solución de 4-metilbencensulfonato de 3-(metiltio)propilo (12.2 g) en metanol (250 ml) se añadió gota a gota una solución de Oxone (marca registrada) (57.7 g) en agua (250 ml) bajo enfriamiento con hielo. Después de completar la adición gota a gota, la mezcla se agitó durante 20 horas mientras se dejaba calentar hasta temperatura ambiente. Se evaporó el metanol a presión reducida, y la mezcla se diluyó con agua. El producto orgánico se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó (Na_2SO_4) y se concentró a presión reducida. Los cristales precipitados se lavaron con acetato de etilo-heptano para dar 4-metilbencensulfonato de 3-(metilsulfonil)propilo (13.1 g, rendimiento: 96%) en forma de cristales incoloros. MS m/z 293 (MH^+).

Ejemplo de referencia 262

A una solución de (2E)-3-(2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.00 g) en N,N-dimetilformamida (50 ml) se añadieron carbonato de potasio (2.67 g) y 4-metilbencensulfonato de 3-(metilsulfonil)propilo (4.46 g), y la mezcla se agitó a 50°C durante 3 h. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, el sólido resultante se recogió por filtración y se lavó con agua para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metilsulfonil)propoxi]fenil}acrilato de etilo (6.34 g, rendimiento: 97%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 190.6-191.0°C.

Ejemplo de referencia 263

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metilsulfonil)propoxi]fenil}acrilato de etilo (6.14 g) en tetrahidrofurano (30 ml) y etanol (30 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (30 ml), y la mezcla se agitó a 50°C durante 3 h. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (30 ml) a la mezcla de reacción, y el sólido resultante se recogió por filtración y se lavó con agua para dar un sólido blanco. El sólido se recristalizó en etanol acuoso para dar ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metilsulfonil)propoxi]fenil}acrílico (4.83 g, rendimiento:

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83%) en forma de cristales blancos. Punto de fusión 202-203°C.

Ejemplos de referencia 264, 26

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (10.0 g) en tetrahidrofurano (300 ml) se añadieron tributilfosfina (10.5 ml), 3-metilbutano-1,3-diol (4.0 ml) y 1.1'-(azodicarbonil)dipiperidina (9.76 g), y la mezcla se agitó durante la noche a 50°C. Luego se añadieron tributilfosfina (10.5 ml), 3-metilbutano-1,3-diol (4.0 ml) y 1.1'-(azodicarbonil)dipiperidina (9.76 g), y la mezcla se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta 45:55, v/v). El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-3-metilbutoxi)fenil]acrilato de etilo (Ejemplo de referencia 264) (1.46 g, rendimiento: 12%) en forma de un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio cristales blancos en forma de 0.5 hidrato. Punto de fusión 63.5-66.0°C.

Luego se obtuvo (2E)-3-[2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-1.1-dimetilpropoxi)fenil]acrilato de etilo (Ejemplo de referencia 265) (0.71 g, rendimiento: 6%) en forma de un aceite anaranjado.

^{1}H-RMN (300 MHz, DMSO-d_6)δ: 1.20 (3 H, t, J = 7.2 Hz), 1.32 (6 H, s), 1.87 (2 H, t, J = 7.5 Hz), 3.55 - 3.62 (2 H, m), 4.12 (2 H, q, J = 7.2 Hz), 4.40 (1 H, t, J = 5.4 Hz), 6.57 (1 H, d, J = 16.2 Hz), 6.96 (1 H, s), 6.94 - 6.99 (1 H, m), 7.55 (1 H, d, J = 16.2 Hz), 8.50 - 8.50 (1 H, m), 8.63 (1 H, d, J = 2.0 Hz).

Ejemplo de referencia 266

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-3-metilbutoxi)fenil]acrilato de etilo (1.20 g) en tetrahidrofurano (3 ml) y etanol (3 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (6.0 ml), y la mezcla se agitó a 50°C durante 30 min. Una solución acuosa 1 N de hidróxido de sodio (1.0 ml) se añadió a la mezcla de reacción, y la mezcla se siguió agitando durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (7.0 ml) a la mezcla de reacción, y se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar un sólido blanco. La recristalización en acetato de

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etilo-hexano dio ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-3-metilbutoxi)fenil]acrílico (957 mg, rendimiento: 85%) en forma de cristales blancos. Punto de fusión 192-194°C.

Ejemplo de referencia 267

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-1.1-dimetilpropoxi)fenil]acrilato de etilo (0.71 g) en acetonitrilo (6 ml) se añadieron diisopropiletilamina (384 µl) y éter clorometilmetílico (170 µl) a temperatura ambiente. Luego se añadieron diisopropiletilamina (384 µl) y éter clorometilmetílico (170 µl) cuatro veces en total cada hora, y la mezcla se siguió agitando a temperatura ambiente durante 1 h. Se añadió agua a la mezcla de reacción y se diluyó con acetato de etilo. La capa orgánica se lavó con agua, ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metoximetoxi)-1.1-dimetilpropoxi]fenil}acrilato de etilo (977 mg, cuant.) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.8 Hz), 1.38 (6 H, s), 1.96 - 2.07 (2 H, m), 3.35 (3 H, s), 3.74 (2 H, t, J = 7.2 Hz), 4.20 (2 H, q, J = 7.1 Hz), 4.62 (2 H, s), 6.40

(1 H, d, J = 16.0 Hz), 6.78 (1 H, d, J = 2.3 Hz), 6.93 (1 H, dd, J = 8.7, 2.3 Hz), 7.60 (1 H, d, J = 8.7 Hz), 7.72 (1 H, d, J = 16.0 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.23 (1 H, d, J = 0.8 Hz).

Ejemplo de referencia 268

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.06 g) en N,N-dimetilformamida (26 ml) se añadieron carbonato de potasio (2.71 g), yoduro de sodio (5.87 g) y óxido de isobutileno (50 ml), y la mezcla se agitó durante la noche a 80°C. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]acrilato de etilo (4.67 g, rendimiento: 78%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 79-83°C.

Ejemplo de referencia 269

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-

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metilpropoxi)fenil]acrilato de etilo (1.77 g) en tetrahidrofurano (6 ml) y etanol (6 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (9 ml), y la mezcla se agitó a 50°C durante 1 hora. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (9 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]acrílico (1.23 g, rendimiento: 74%) en forma de cristales blancos. Punto de fusión 126.5-128.0°C.

Ejemplo de referencia 270

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.10 g) en N,N-dimetilformamida (26 ml) se añadieron carbonato de potasio (2.75 g), yoduro de sodio (5.90 g) y 1-bromo-3-metoxipropano (2.61 g), y la mezcla se agitó a 50°C durante 1 hora. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía

en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]acrilato de etilo (4.22 g, rendimiento: 70%) en forma de cristales blancos. Punto de fusión 86.4-86.5°C.

Ejemplo de referencia 271

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]acrilato de etilo (2.38 g) en tetrahidrofurano (6 ml) y etanol (6 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (12 ml), y la mezcla se agitó a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (12 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]acrílico (1.47 g, rendimiento: 76%) en forma de cristales blancos. Punto de fusión 131-133°C.

Ejemplo de referencia 272

A una solución de [2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (11.5 g) en piridina (25 ml) se añadió anhídrido acético (25 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar acetato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (8.80 g, rendimiento: 76%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 52.5-53.0°C.

Ejemplo de referencia 273

A una solución de acetato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (1.80 g) en tolueno (20 ml) se añadieron dimetilquitina metil trimetil acetal (3.50 ml) y perclorato de magnesio (1.44 g), y la mezcla se agitó a 50°C durante 3 h. Se añadió agua a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se

sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetilpropanoato de metilo (1.78 g, rendimiento: 90%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.17 (6 H, s), 2.73 (2 H, s), 3.43 (3 H, s), 3.66 (3 H, s), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.08 (2 H, dd, J = 5.5, 4.0 Hz), 6.66 (1 H, d, J = 2.4 Hz), 6.80 (1 H, dd, J = 8.6, 2.5 Hz), 7.15 - 7.24 (1 H, m), 7.98 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.3, 0.9 Hz).

Ejemplo de referencia 274

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetilpropanoato de metilo (1.75 g) en tetrahidrofurano (4 ml) se añadió ácido sulfúrico concentrado-ácido acético-agua (1:6:6, v/v, 8 ml), y la mezcla se agitó a 80°C durante 24 h. Tras dejar enfriar hasta temperatura ambiente, la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetilpropanoico (1.36 g, rendimiento: 80%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.20 (6 H, s), 2.77 (2 H, s), 3.43 (3 H, s), 3.73 (2 H, dd, J = 5.0, 3.9 Hz), 4.04 - 4.12 (2 H, m), 6.67 (1 H, d, J = 1.9 Hz), 6.81 (1 H, dd, J = 8.6, 1.6 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, s), 8.25 (1 H, d, J = 0.9 Hz).

Ejemplo de referencia 275

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.17 g) en N,N-dimetilformamida (30 ml) se añadieron carbonato de potasio (3.64 g), yoduro de sodio (3.99 g) y bromuro de 3-(2-metoxietoxi)propilo (5.25 g), y la mezcla se agitó durante la noche a 50°C. Tras dejar enfriar hasta temperatura ambiente, se añadió una solución acuosa saturada de cloruro de amonio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}acrilato de etilo (5.34 g, rendimiento: 80%) en forma de cristales blancos. Punto de fusión 65-67°C.

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Ejemplo de referencia 276

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}acrilato de etilo (2.92 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (13 ml), y la mezcla se agitó a 50°C durante 20 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (13 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}acrílico (2.56 g, rendimiento: 93%) en forma de cristales blancos. Punto de fusión 103.0-104.0°C.

Ejemplo de referencia 277

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.12 g) en N,N-dimetilformamida (30 ml) se añadieron carbonato de potasio (3.66 g), yoduro de sodio (3.89 g) y 1-bromo-2-(2-metoxietoxi)etano (3.60 ml), y la mezcla se agitó durante la noche a 50°C. Luego se añadieron carbonato de potasio (7.21 g) y 1-bromo-2-(2-metoxietoxi)etano (7.20 ml), y la mezcla se siguió agitando durante 4 h. Tras dejar enfriar

hasta temperatura ambiente, se añadió una solución acuosa saturada de cloruro de amonio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metoxietoxi)etoxi]fenil}acrilato de etilo (5.57 g, rendimiento: 86%) en forma de cristales blancos. Punto de fusión 76.6-76.8°C.

Ejemplo de referencia 278

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metoxietoxi)etoxi]fenil}acrilato de etilo (3.32 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (15 ml), y la mezcla se agitó a 50°C durante 20 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (15 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-

4-[2-(2-metoxietoxi)etoxi]fenil}acrílico (2.01 g, rendimiento: 64%) en forma de cristales blancos. Punto de fusión 133.9-134.0°C.

Ejemplo de referencia 279

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]acrílico (1.33 g) en tetrahidrofurano (40 ml) se añadió un complejo de paladio-carbón activado-etilenodiamina (0.20 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. La mezcla de reacción se filtró, se añadió un complejo de paladio-carbón activado-etilenodiamina (0.41 g) al filtrado, y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. Se añadió metanol (40 ml) a la mezcla de reacción, y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propanoico (571 mg, rendimiento: 43%) en forma de cristales blancos. Punto de fusión 99.1-99.2°C.

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Ejemplo de referencia 280

A una solución de 2,4-dihidroxibenzaldehído (24.5 g) en acetonitrilo (200 ml) se añadieron bicarbonato de potasio (35.5 g) y 3-bromo-1-propanol (49.3 g), y la mezcla se agitó a 80°C durante 3 días. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar 2-hidroxi-4-(3-hidroxipropoxi)benzaldehído (14.2 g, rendimiento: 41%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.01 - 2.12 (2 H, m), 3.87 (2 H, q, J = 5.7 Hz), 4.18 (2 H, t, J = 6.1 Hz), 6.44 (1 H, d, J = 2.4 Hz), 6.54 (1 H, dd, J = 8.7, 2.3 Hz), 7.43 (1 H, d, J = 8.7 Hz), 9.72 (1 H, s), 11.47 (1 H, s).

Ejemplo de referencia 281

A una solución de 2-hidroxi-4-(3-hidroxipropoxi)benzaldehído (6.90 g) en acetona (170 ml) se añadió carbonato de potasio (5.83 g) y éter clorometilmetílico (3.20 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante la noche mientras se dejaba calentar hasta temperatura ambiente. Luego se añadieron carbonato de potasio (5.83 g) y éter clorometilmetílico (3.20 ml), y la mezcla se agitó a

temperatura ambiente durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:2, v/v) para dar un 4-(3-hidroxipropoxi)-2-(metoximetoxi)benzaldehído (4.67 g, rendimiento: 55%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.53 - 1.62 (1 H, m), 1.97 - 2.12 (2 H, m), 3.53 (3 H, s), 3.87 (2 H, q, J = 5.7 Hz), 4.19 (2 H, t, J = 6.0 Hz), 5.29 (2 H, s), 6.62 (1 H, dd, J = 8.4, 2.0 Hz), 6.72 (1 H, d, J = 2.3 Hz), 7.81 (1 H, d, J = 8.9 Hz), 10.33 (1 H, s).

Ejemplo de referencia 282

A una solución de 4-(3-hidroxipropoxi)-2-(metoximetoxi)benzaldehído (2.02 g) en N,N-dimetilformamida (40 ml) se añadió hidruro de sodio (60% en aceite, 404 mg) bajo agitación con enfriamiento con hielo, y se añadió bromometilciclopropano (1.70 ml) 30 min más tarde, y la mezcla se agitó durante la noche a temperatura ambiente. Luego se añadieron hidruro de sodio (60% en aceite, 404 mg) y bromometilciclopropano (1.70 ml) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 3 horas y a 50°C durante 2 h. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se diluyó con

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acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar 4-[3-(ciclopropilmetoxi)propoxi]-2-(metoximetoxi)benzaldehído (1.16 g, rendimiento: 47%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.15 - 0.23 (2 H, m), 0.46 - 0.63 (2 H, m), 0.87 - 1.14 (1 H, m), 2.01 - 2.16 (2 H, m), 3.28 (2 H, d, J = 6.8 Hz), 3.53 (3 H, s), 3.62 (2 H, t, J = 6.2 Hz), 4.10 - 4.16 (2 H, m), 5.28 (2 H, s), 6.53 - 6.65 (1 H, m), 6.70 (1 H, d, J = 2.3 Hz), 7.81 (1 H, d, J = 8.7 Hz), 10.32 (1 H, s).

Ejemplo de referencia 283

A una solución de fosfonoacetato de trietilo (1.06 g) en tetrahidrofurano (5 ml) se añadió hidruro de sodio (60% en aceite, 189 mg) bajo enfriamiento con hielo, se agregó una solución de 4-[3-(ciclopropilmetoxi)propoxi]-2-(metoximetoxi)benzaldehído (1.16 g) en N,N-dimetilformamida (5 ml) gota a gota 30 min más tarde, y la mezcla se agitó durante 20 min mientras se dejaba calentar hasta temperatura ambiente. Luego se añadieron fosfonoacetato de trietilo (1.06 g) e hidruro de sodio (60% en aceite, 189 mg) a temperatura ambiente, y la mezcla se siguió agitando durante 20 min. Una solución acuosa saturada de cloruro de amonio se añadió a la

hasta 2:3, v/v) para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(ciclopropilmetoxi)propoxi]fenil}acrilato de etilo (0.66 g, rendimiento: 34%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.14 - 0.23 (2 H, m), 0.45 - 0.57 (2 H, m), 0.88 - 1.11 (1 H, m), 1.28 (3 H, t, J = 7.1 Hz), 2.06 (2 H, tt, J = 6.2, 6.2 Hz), 3.26 (2 H, d, J = 6.8 Hz), 3.60 (2 H, t, J = 6.1 Hz), 4.09 (2 H, t, J = 6.0 Hz), 4.20 (2 H, q, J = 7.2 Hz), 6.36 (1 H, d, J = 16.0 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.87 (1 H, dd, J = 8.6, 2.4 Hz), 7.63 (1 H, d, J = 8.9 Hz), 7.69 (1 H, d, J = 16.0 Hz), 8.01 (1 H, d, J = 1.7 Hz), 8.25 (1 H, dd, J = 2.3, 0.9 Hz).

Ejemplo de referencia 284

A una solución de 2,4-dihidroxi-3-metilbenzoato de metilo (14.8 g) en acetona (200 ml) se añadieron carbonato de potasio (22.4 g) y éter clorometilmetílico (9.0 ml), y la mezcla se agitó bajo enfriamiento con hielo durante 2 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 2-hidroxi-4-(metoximetoxi)-3-metilbenzoato de metilo (11.9 g, rendimiento: 65%) en forma de cristales blancos. Punto de fusión 73.8-74.0°C.

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Ejemplo de referencia 285

A una solución de 2-hidroxi-4-(metoximetoxi)-3-metilbenzoato de metilo (1.97 g) en N,N-dimetilformamida (16 ml) se añadieron carbonato de potasio (2.41 g) y cloruro de 2,4-diclorobencilo (1.50 ml), y la mezcla se agitó durante la noche a 50°C. Se añadió agua a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en hexano dio 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoato de metilo (3.01 g, rendimiento: 90%) en forma de cristales blancos. Punto de fusión 98.8-99.0°C. Se obtuvo un producto crudo del agua madre (0.73 g).

Ejemplo de referencia 286

A una solución de 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoato de metilo (2.91 g) en tetrahidrofurano (8 ml) y metanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (16 ml), y la mezcla se agitó durante la noche a 50°C. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ácido 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoico (2.67 g,

rendimiento: 95%) en forma de cristales blancos. Punto de fusión 173.5-174.0°C.

A una solución de un producto crudo de 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoato de metilo (Ejemplo de referencia 285, 0.73 g) en tetrahidrofurano (2 ml) y metanol (2 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4 ml), y la mezcla se agitó durante la noche a 50°C. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio un producto crudo (221 mg, rendimiento: 31%) de ácido 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoico en forma de cristales blancos.

Ejemplo de referencia 287

A una solución de ácido 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoico (2.59 g) en N,N-dimetilformamida (60 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (2.01 g), trietilamina (2.90 ml), clorhidrato de N,O-dimetilhidroxilamina (1.11 g), e hidrato de 1-hidroxibenzotriazol (612 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se

extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un producto crudo en forma de un aceite amarillo.

A una solución de un producto crudo de ácido 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzoico (Ejemplo de referencia 57, 221 mg) en N,N-dimetilformamida (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (170 mg), trietilamina (0.25 ml), clorhidrato de N,O-dimetilhidroxilamina (112 mg), e hidrato de 1-hidroxibenzotriazol (137 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un producto crudo en forma de un aceite amarillo.

Se combinaron los productos crudos obtenidos, se sometieron a cromatografía en columna de gel de sílice, y se eluyeron con acetato de etilo-hexano (15:85 - 1:1, v/v) para dar 2-[(2,4-diclorobencil)oxi]-N-metoxi-4-(metoximetoxi)-N,3-dimetilbenzamida (3.04 g, rendimiento: 97%) en forma de un aceite incoloro.

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^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.18 (3 H, s), 3.23 (3 H, s), 3.50 (3 H, s), 3.57 (3 H, br. s.), 5.00 (2 H, s), 5.23 (2 H, s), 6.92 (1 H, d, J = 8.5 Hz), 7.15 (1 H, d, J = 8.5 Hz), 7.25 - 7.31 (1 H, m), 7.40 (1 H, d, J = 2.1 Hz), 7.58 (1 H, d, J = 8.3 Hz).

Ejemplo de referencia 288

A una solución de 2-[(2,4-diclorobencil)oxi]-N-metoxi-4-(metoximetoxi)-N,3-dimetilbenzamida (3.04 g) en tetrahidrofurano (35 ml) se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (7.5 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. Luego bajo enfriamiento con hielo, se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (7.5 ml), y la mezcla se agitó durante la noche mientras se dejaba calentar hasta temperatura ambiente. Bajo enfriamiento con hielo, se añadió una solución acuosa saturada de cloruro de amonio (4.3 ml) gota a gota a la mezcla de reacción, y la mezcla se agitó durante 1 hora. La mezcla se filtró a través de celite, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzaldehído (1.61 g, rendimiento: 62%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 128.4-128.5°C.

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Ejemplo de referencia 289

A una solución de fosfonoacetato de trietilo (1.06 g) en tetrahidrofurano (5 ml) se añadió hidruro de sodio (60% en aceite, 189 mg) bajo enfriamiento con hielo, y 30 min más tarde, se añadió una solución de 2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilbenzaldehído (1.40 g) en N,N-dimetilformamida (5 ml) gota a gota, y la mezcla se agitó durante 10 min mientras se dejaba calentar hasta temperatura ambiente. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilfenil]acrilato de etilo (1.79 g, cuant.) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 110-112°C.

Ejemplo de referencia 290

A una solución de (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(metoximetoxi)-3-metilfenil]acrilato de etilo (1.79 g) en acetona (16 ml) se añadió ácido clorhídrico 1 N (8 ml), y la mezcla se agitó durante la noche con calentamiento a reflujo. Tras dejar enfriar hasta temperatura ambiente, una solución acuosa 1 N de hidróxido de sodio (8 ml) se añadió a la mezcla de reacción. El sólido resultante se recogió por filtración y se lavó con agua fría para dar (2E)-

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3-{2-[(2,4-diclorobencil)oxi]-4-hidroxi-3-metilfenil}acrilato de etilo (0.43 g, rendimiento: 29%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.31 (3 H, t, J = 7.2 Hz), 2.19 (3 H, s), 4.23 (2 H, q, J = 7.2 Hz), 4.88 (2 H, s), 5.16 (1 H, br. s.), 6.31 (1 H, d, J = 16.0 Hz), 6.66 (1 H, d, J = 8.5 Hz), 7.32 (1 H, dd, J = 8.3, 2.1 Hz), 7.36 (1 H, d, J = 8.7 Hz), 7.44 (1 H, d, J = 2.1 Hz), 7.59 (1 H, d, J = 8.3 Hz), 7.91 (1 H, d, J = 16.2 Hz).

Ejemplo de referencia 291

A una solución de (2E)-3-{2-[(2,4-diclorobencil)oxi]-4-hidroxi-3-metilfenil}acrilato de etilo (0.43 g) en N,N-dimetilformamida (10 ml) se añadieron carbonato de potasio (0.47 g), yoduro de sodio (0.51 g) y éter 2-bromoetilmetílico (0.47 g), y la mezcla se agitó durante la noche a 50°C y a 80°C durante 2 h. Luego se agregaron carbonato de potasio (0.47 g), yoduro de sodio (0.51 g) y éter 2-bromoetilmetílico (0.47 g), y la mezcla se siguió agitando durante 2 h. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:7, v/v) para dar (2E)-3-[2-[(2,4-

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diclorobencil)oxi]-4-(2-metoxietoxi)-3-metilfenil]acrilato de etilo (180 mg, rendimiento: 36%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 92.0-92.5°C.

Ejemplo de referencia 292

A una solución de (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)-3-metilfenil]acrilato de etilo (170 mg) en tetrahidrofurano (2 ml) y etanol (2 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (6.0 ml), y la mezcla se agitó durante la noche a 80°C. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (6.0 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar ácido (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)-3-metilfenil]acrílico (99 mg, rendimiento: 24%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos.

^{1}H-RMN (300 MHz, DMSO-d_6)δ:2.10 (3 H, s), 3.30 (3 H, s), 3.58 - 3.75 (2 H, m), 4.12 - 4.21 (2 H, m), 4.84 (2 H, s), 6.36 (1 H, d, J = 16.0 Hz), 6.88 (1 H, d, J = 8.7 Hz), 7.46 - 7.53 (1 H, m), 7.62 (2 H, d, J = 8.3 Hz), 7.69 (1 H, d, J = 2.1 Hz), 7.74 (1 H, d, J = 16.0 Hz).

Ejemplo de referencia 293

A una solución de (2E)-3-(2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (2.53 g) en tetrahidrofurano (100 ml) se añadieron tributilfosfina (3.30 ml), 2-(ciclopropiloxi)etanol (0.80 g) y 1.1'-(azodicarbonil)dipiperidina (2.47 g), y la mezcla se agitó a 50°C durante 30 min. La mezcla de reacción se concentró, el sólido obtenido se lavó con éter diisopropílico, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 35:65, v/v) para dar una (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}acrilato de etilo (2.21 g, rendimiento: 72%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 75.4-75.9°C.

Ejemplo de referencia 294

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}acrilato de etilo (2.01 g) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (10 ml), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N (10 ml) a la mezcla de reacción, y se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-

2-il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}acrílico (1.83 g, rendimiento: 97%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 147-150°C.

Ejemplo de referencia 295

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (5.12 g) en tetrahidrofurano (40 ml) se añadió un complejo de paladio-carbón activado-etilenodiamina (0.23 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. La mezcla de reacción se filtró, se añadió un complejo de paladio-carbón activado-etilenodiamina (0.50 g) al filtrado, y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. Luego se agregó metanol (40 ml), y la mezcla se siguió agitando bajo una atmósfera de hidrógeno a temperatura ambiente durante 15 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un aceite anaranjado.

A una solución del aceite obtenido en N,N-dimetilformamida (30 ml) se añadieron carbonato de potasio (1.79 g), yoduro de sodio (1.95 g) y 2-(2-bromoetil)-2-metil-1,3-dioxolano (1.78 ml), y la mezcla se agitó durante la noche

a 60°C. Tras dejar enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}propanoato de etilo (0.77 g, rendimiento: 19%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.21 (3 H, t, J = 7.1 Hz), 1.38 (3 H, s), 2.15 (2 H, t, J = 7.0 Hz), 2.56 (2 H, t, J = 7.5 Hz), 2.76 (2 H, t, J = 7.7 Hz), 3.85 - 4.00 (4 H, m), 4.01 - 4.15 (4 H, m), 6.65 (1 H, d, J = 2.6 Hz), 6.79 (1 H, dd, J = 8.5, 2.4 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 296

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (875 mg) en N,N-dimetilformamida (8 ml) se añadieron carbonato de potasio (695 mg) y 3-cloro-4-nitrobenzotrifluoruro (894 mg), y la mezcla se agitó a 50°C durante 3 h. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$),

se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar un sólido de color marrón. La recristalización en acetato de etilo-hexano dio (2E)-3-{4-(2-metoxietoxi)-2-[2-nitro-5-(trifluorometil)fenoxi]fenil}acrilato de etilo (0.97 g, rendimiento: 65%) en forma de cristales de color marrón rojizo. Punto de fusión 108-110°C.

Ejemplo de referencia 297

A una solución de 3-[2-hidroxi-4-(2-metoxietoxi)fenil]propanoato de etilo (8.98 g) en N,N-dimetilformamida (60 ml) se añadieron carbonato de potasio (9.25 g) y bromuro de bencilo (5.0 ml), y la mezcla se agitó a temperatura ambiente durante 3 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta 35:65, v/v) para dar un aceite incoloro. El aceite se disolvió en acetato de etilo, y la solución se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar 3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]propanoato de etilo (11.5 g, rendimiento: 96%) en forma de un sólido blanco. La recristalización en

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acetato de etilo-hexano dio cristales blancos. Punto de fusión 38-39°C.

Ejemplo de referencia 298

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]acrilato de etilo (2.44 g) en tetrahidrofurano (50 ml) se añadió paladio-carbón activado al 10% (1.06 g), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar un aceite amarillo.

A una solución del aceite obtenido en tetrahidrofurano (30 ml) se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (12 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 20 min. Bajo enfriamiento con hielo, se añadió una solución acuosa saturada de cloruro de amonio gota a gota a la mezcla de reacción, y la mezcla se agitó durante 1 hora. La mezcla se filtró a través de celite, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]propan-1-ol (1.10 g,

rendimiento: 45%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 81.2-82.0°C.

Ejemplo de referencia 299

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo en diclorometano (100 ml) se añadieron piridina (25.0 ml) y anhídrido tríflico (6.0 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 5 min. Se añadió agua a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta 35:65, v/v) para dar (2E)-3-(4-(2-metoxietoxi)-2-{[(trifluorometil)sulfonil]oxi}fenil)acrilato de etilo (12.56 g, cuant.) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 37.1-37.3°C.

Ejemplo de referencia 300

Una mezcla de (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (2.96 g), un complejo de paladio-carbón activado-etilenodiamina (0.30 g) y metanol (200 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. El catalizador se filtró, y

el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propanoato de etilo (2.04 g, rendimiento: 69%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 2.56 (2 H, t, J = 7.6 Hz), 2.78 (2 H, t, J = 7.8 Hz), 3.45 (3 H, s), 3.65 - 3.79 (2 H, m), 4.03 - 4.15 (4 H, m), 6.64 (1 H, d, J = 2.7 Hz), 6.77 (1 H, dd, J = 8.7, 2.7 Hz), 7.20 (1 H, d, J = 8.3 Hz), 7.77 (1 H, d, J = 2.7 Hz), 7.95 (1 H, d, J = 2.3 Hz).

Ejemplo de referencia 301

Se disolvió 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propanoato de etilo (2.04 g) en éter dietílico (9.8 ml), se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (8.2 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadieron metanol y agua a la mezcla de reacción, la mezcla se agitó durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 3:2, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propan-1-ol

(1.48 g, rendimiento: 81%) en forma de cristales incoloros. Punto de fusión 83.9-84.5°C.

Ejemplo de referencia 302

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}acrilato de etilo (1.00 g) en tetrahidrofurano (10 ml) se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (4.97 ml) bajo enfriamiento con hielo durante 15 min, y la mezcla se agitó durante 1 hora. La mezcla de reacción se agitó a temperatura ambiente durante 2 h, se añadió sulfato de sodio decahidratado (2.40 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 12 h. El material insoluble se filtró y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:3, v/v) para dar un sólido blanco. La recristalización en éter dietílico-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}prop-2-en-1-ol (40 mg, rendimiento: 4%) en forma de un polvo blanco. Punto de fusión 52.5-54.5°C.

Ejemplo de referencia 303

Una mezcla de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}prop-2-en-1-ol (135 mg), paladio-carbón al 5% (16 mg) y acetato de etilo (5 ml) se agitó bajo

una atmósfera de hidrógeno a temperatura ambiente durante 2.5 h. Se filtró el paladio, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:3, v/v) para dar 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}propan-1-ol (120 mg, rendimiento: 88%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.17 (6 H, t, J = 7.0 Hz), 1.75 - 1.91 (2 H, m), 2.46 - 2.63 (2 H, m), 3.45 - 3.57 (4 H, m), 3.57 - 3.71 (6 H, m), 4.38 - 4.51 (1 H, m), 6.74 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 8.5, 2.5 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, dd, J = 2.2, 0.5 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 304

Una suspensión de (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrilato de etilo (2.52 g) y paladio sobre carbón al 10% en etanol se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. La mezcla de reacción se filtró, y el solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 2:8, v/v) para dar 3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}fenil)propanoato de etilo (1.88 g, rendimiento: 74%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.04 (9 H, s), 1.14 - 1.32 (4 H, m), 2.57 (2 H, t, J = 7.8 Hz), 2.76 (2 H, t, J = 7.8 Hz), 3.89 - 4.19 (6 H, m), 6.63 (1 H, d, J = 2.7 Hz), 6.76 (1 H, dd, J = 8.5, 2.5 Hz), 7.21 (1 H, d, J = 8.7 Hz), 7.31 - 7.47 (6 H, m), 7.63 - 7.77 (4 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.25 (1 H, s).

Ejemplo de referencia 305

Bajo enfriamiento con hielo, a una solución de 3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propanoato de etilo (1.88 g) en éter dietílico (10 ml) se añadió gota a gota una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (5.6 ml), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 4 h. Se añadió salmuera saturada a la mezcla de reacción, la mezcla se filtró, y el filtrado se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 6:4, v/v) para dar 3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propan-1-ol (1.06 g, rendimiento: 60%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.04 (9 H, s), 1.36 (1 H, t,

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J = 5.7 Hz), 1.75 - 1.89 (2 H, m), 2.53 (2 H, t, J = 7.5 Hz), 3.61 (2 H, q, J = 6.1 Hz), 3.93 - 4.08 (4 H, m), 6.62 (1 H, d, J = 2.6 Hz), 6.78 (1 H, dd, J = 8.5, 2.6 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.31 - 7.46 (6 H, m), 7.64 - 7.75 (4 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.25 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 306

Bajo enfriamiento con hielo, a una solución de ácido 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propanoico (6.00 g) y trietilamina (2.26 g) en tetrahidrofurano (100 ml) se añadió isobutilcloroformiato (2.24 g), y la mezcla se agitó durante 10 min. A la misma temperatura, se añadieron metanol (50 ml), agua (50 ml) y borohidruro de sodio (1.41 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 1 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v) para dar 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propan-1-ol (3.86 g, rendimiento: 66%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.2 Hz), 1.75 - 1.90 (2 H, m), 2.54 (2 H, t, J = 7.5 Hz), 3.61 (2 H, t, J = 6.3 Hz), 4.40 - 4.56 (1 H, m), 6.61 (1 H, d, J = 2.4 Hz),

6.78 (1 H, dd, J = 8.5, 2.4 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 1.7 Hz), 8.23 - 8.30 (1 H, m).

Ejemplo de referencia 307

Bajo enfriamiento con hielo, a una solución mixta de 2-(benciloxi)-4-(2-metoxietoxi)benzaldehído (5.00 g) y cloroacetato de etilo (1.85 ml) en tetrahidrofurano (60 ml)/ter-butanol (20 ml) se añadió ter-butóxido de potasio (2.14 g), y la mezcla se agitó a la misma temperatura durante 1 h. Una solución acuosa 1 N de hidróxido de sodio (20 ml) se agregó, y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 2 h. Se añadió ácido acético (10 ml), y la mezcla se agitó a 50°C durante 4 h. La solución de reacción se dejó enfriar hasta temperatura ambiente, se añadieron una solución acuosa 1 N de hidróxido de sodio y acetato de etilo, y la mezcla se lavó sucesivamente con agua y una solución acuosa saturada de carbonato ácido de sodio. La capa orgánica se secó ($MgSO_4$), y el solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v) para dar [2-(benciloxi)-4-(2-metoxietoxi)fenil]acetaldehído (1.80 g, rendimiento: 34%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.45 (3 H, s), 3.62 (2 H, d, J = 2.1 Hz), 3.70 - 3.78 (2 H, m), 4.07 - 4.15 (2 H, m), 5.05 (2 H, s), 6.50 (1 H, dd, J = 8.3, 2.4 Hz), 6.62 (1 H, d, J =

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2.3 Hz), 7.05 (1 H, d, J = 8.3 Hz), 7.28 - 7.43 (5 H, m), 9.68 (1 H, t, J = 2.1 Hz).

Ejemplo de referencia 308

Bajo enfriamiento con hielo, a una mezcla de [2-(benciloxi)-4-(2-metoxietoxi)fenil]acetaldehído (1.80 g), metanol (25 ml) y agua (25 ml) se añadió borohidruro de sodio (0.34 g) en pequeñas porciones, y la mezcla se agitó a la misma temperatura durante 2 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, se evaporó el metanol a presión reducida, y el residuo se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 7:3, v/v) para dar 2-[2-(benciloxi)-4-(2-metoxietoxi)fenil]etanol (1.50 g, rendimiento: 83%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.88 (2 H, t, J = 6.4 Hz), 3.45 (3 H, s), 3.70 - 3.76 (2 H, m), 3.81 (2 H, t, J = 6.3 Hz), 4.06 - 4.13 (2 H, m), 5.04 (2 H, s), 6.47 (1 H, dd, J = 8.3, 2.4 Hz), 6.60 (1 H, d, J = 2.4 Hz), 7.08 (1 H, d, J = 8.3 Hz), 7.28 - 7.48 (5 H, m).

Ejemplo de referencia 309

Bajo enfriamiento con hielo, a una solución mixta de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)benzaldehído (10.0 g) y bromoacetato de etilo

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(11.6 g) en tetrahidrofurano (100 ml)/ter-butanol (100 ml) se añadió ter-butóxido de potasio (7.78 g), y la mezcla se agitó a la misma temperatura durante 12 h. El solvente se evaporó a presión reducida, se añadieron solución acuosa 8 N de hidróxido de sodio (17 ml), agua (34 ml) y tetrahidrofurano (50 ml) al residuo, y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió ácido acético (200 ml), y la mezcla se agitó a 60°C durante 4 h. La solución de reacción se dejó enfriar hasta temperatura ambiente, y se neutralizó con una solución acuosa 8 N de hidróxido de sodio y se añadió acetato de etilo. La mezcla se lavó sucesivamente con agua y una solución acuosa saturada de carbonato ácido de sodio. La capa orgánica se secó ($MgSO_4$), y el solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 4:6, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]acetaldehído (2.07 g, rendimiento: 20%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.48 (3 H, s), 3.54 (2 H, d, J = 1.9 Hz), 5.18 (2 H, s), 6.91 (1 H, d, J = 2.7 Hz), 7.00 (1 H, dd, J = 8.5, 2.5 Hz), 7.22 - 7.28 (1 H, m), 7.99 (1 H, d, J = 1.9 Hz), 8.25 (1 H, s), 9.67 (1 H, t, J = 2.1 Hz).

Ejemplo de referencia 310

Bajo enfriamiento con hielo, a una mezcla de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]acetaldehído (1.54 g), metanol (60 ml) y agua (25 ml) se añadió borohidruro de sodio (0.23 g) en pequeñas porciones, y la mezcla se agitó a la misma temperatura durante 2 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, se evaporó el metanol a presión reducida, y el residuo se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v) para dar 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]etanol (1.32 g, rendimiento: 85%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.49 - 1.58 (1 H, m), 2.75 (2 H, d), 3.47 (3 H, d), 3.80 (2 H, d), 5.15 (2 H, d), 6.81 (1 H, d, J = 2.4 Hz), 6.96 (1 H, dd, J = 8.5, 2.4 Hz), 7.22 - 7.32 (1 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 311

A {[(2-isopropoxietil)amino]sulfonil}carbamato de 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]etilo (0.19 g) se añadió una solución metanólica al 10% de ácido clorhídrico (5 ml), y la mezcla se

agitó a 40°C durante 3 h. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 2-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)etilo (0.085 g, rendimiento: 48%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.15 (6 H, d, J = 6.0 Hz), 2.87 (2 H, t, J = 6.7 Hz), 3.13 (2 H, q, J = 5.7 Hz), 3.44 - 3.65 (3 H, m), 4.36 (2 H, t, J = 6.6 Hz), 5.21 (1 H, s), 5.28 - 5.41 (1 H, m), 6.59 (1 H, d, J = 2.6 Hz), 6.73 (1 H, dd, J = 8.4, 2.5 Hz), 7.19 (1 H, d, J = 8.5 Hz), 7.61 (1 H, s), 8.03 (1 H, d, J = 2.1 Hz), 8.32 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 312

Una suspensión de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]acrilato de etilo (9.5 g) y paladio sobre carbón al 10% en etanol (300 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. La mezcla de reacción se filtró, y el solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de

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gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 2:8, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propanoato de etilo (8.1 g, rendimiento: 85%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.17 - 1.30 (3 H, t, J = 7.2 Hz), 2.52 - 2.62 (2 H, m), 2.77 (2 H, t, J = 7.6 Hz), 3.47 (3 H, s), 4.09 (2 H, q, J = 7.2 Hz), 5.15 (2 H, s), 6.81 (1 H, d, J = 2.3 Hz), 6.88 - 6.99 (1 H, m), 7.24 (1 H, d, J = 8.3 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, s).

Ejemplo de referencia 313

Bajo enfriamiento con hielo, a una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propanoato de etilo (8.0 g) en éter dietílico (30 ml) se añadió gota a gota una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (36.8 ml), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 4 h. Se añadió salmuera saturada a la mezcla de reacción, la mezcla se filtró, y el filtrado se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propan-1-ol (5.18 g, rendimiento: 72%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.36 (1 H, t, J = 5.6 Hz), 1.75 - 1.91 (2 H, m), 2.48 - 2.60 (2 H, m), 3.48 (3 H, s), 3.61 (2 H, q, J = 6.2 Hz), 5.15 (2 H, s), 6.80 (1 H, d, J = 2.4 Hz), 6.94 (1 H, dd, J = 8.5, 2.4 Hz), 7.24 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo de referencia 314

A {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propilo (5.2 g) se añadió una solución metanólica al 10% de ácido clorhídrico (50 ml), y la mezcla se agitó a 40°C durante 3 h. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 6:4, v/v) para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propilo (3.9 g, rendimiento: 81%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.17 (6 H, d, J = 6.1 Hz), 1.86 - 2.02 (2 H, m), 2.62 (2 H, t, J = 7.4 Hz), 3.24 (2 H, q, J = 5.6 Hz), 3.50 - 3.70 (3 H, m), 4.13 (2 H, t, J = 6.1 Hz), 5.34 (1 H, t, J = 5.9 Hz), 5.48 (1 H, br.s.), 6.64 (1 H, d, J

= 2.3 Hz), 6.71 (1 H, dd, J = 8.1, 2.5 Hz), 7.14 (1 H, d, J = 8.3 Hz), 7.92 (1 H, br.s.), 8.03 (1 H, d, J = 2.3 Hz), 8.31 (1 H, s).

Ejemplo de referencia 315

Una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (3.00 g), 4-bromobutironitrilo (1.72 g), carbonato de potasio (2.14 g), yoduro de sodio (1.74 g) y N,N-dimetilformamida (20 ml) se agitó a 50°C durante 15 h. Tras enfriar, la mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-cianopropoxi)fenil]acrilato de etilo (3.30 g, rendimiento: 94%) en forma de cristales incoloros. Punto de fusión 106-107°C.

Ejemplo de referencia 316

Una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (3.00 g), 2-(2-bromoetil)-2-metil-1,3-dioxolano (2.27 g), carbonato de potasio (2.14 g), yoduro de sodio (1.74 g), y N,N-dimetilformamida (20 ml) se agitó a 50°C durante 15 horas y a 80°C durante 6 h. Tras enfriar, la mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo.

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La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}acrilato de etilo (2.86 g, rendimiento: 74%) en forma de cristales incoloros. Punto de fusión 90-91°C.

Ejemplo de referencia 317

Una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (3.00 g), bromoacetona (1.59 g), carbonato de potasio (2.14 g), yoduro de sodio (1.74 g) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2*E*)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-oxopropoxi)fenil]acrilato de etilo (2.77 g, rendimiento: 81%) en forma de cristales incoloros. Punto de fusión 167-168°C.

Ejemplo de referencia 318

Una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de

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etilo (3.00 g), éter glicidilisopropílico (4.50 g), carbonato de potasio (6.42 g), yoduro de sodio (5.80 g), y N,N-dimetilformamida (20 ml) se agitó a 50°C durante 15 horas y a 80°C durante 6 h. Tras enfriar, la mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v) para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-3-isopropoxipropoxi)fenil]acrilato de etilo (3.16 g, rendimiento: 81%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.17 (6 H, d, J = 6.3 Hz), 1.28 (3 H, t, J = 7.2 Hz), 2.54 (1 H, d, J = 4.5 Hz), 3.48 - 3.68 (3 H, m), 4.00 - 4.24 (5 H, m), 6.37 (1 H, d, J = 16.2 Hz), 6.72 (1 H, s), 6.78 - 6.93 (1 H, m), 7.61 - 7.72 (2 H, m), 8.02 (1 H, s), 8.25 (1 H, s).

Ejemplo de referencia 319

A una mezcla de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-cianopropoxi)fenil]acrilato de etilo (3.25 g), tetrahidrofurano (15 ml) y etanol (10 ml) se añadió una solución 1 M de hidróxido de sodio (14.3 ml), y la mezcla se agitó a 50°C durante 2 h. La mezcla de reacción se vertió en agua, y la mezcla se neutralizó con una solución 1 M de ácido

clorhídrico (14.4 ml) y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-cianopropoxi)fenil]acrílico (2.38 g, rendimiento: 78%) en forma de cristales incoloros. Punto de fusión 183-185°C.

Ejemplo de referencia 320

A una mezcla de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-oxopropoxi)fenil]acrilato de etilo (2.46 g), tetrahidrofurano (40 ml) y etanol (10 ml) se añadió una solución 1 M de hidróxido de sodio (11.1 ml), y la mezcla se agitó a 50°C durante 3 h. La mezcla de reacción se vertió en agua, y la mezcla se neutralizó con una solución 1 M de ácido clorhídrico (11.2 ml) y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-oxopropoxi)fenil]acrílico (311 mg, rendimiento: 14%) en forma de cristales incoloros. Punto de fusión 179-180°C.

Ejemplo de referencia 321

A una mezcla de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-

2-il)etoxi]fenil}acrilato de etilo (2.75 g), tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución 1 M de hidróxido de sodio (11.0 ml), y la mezcla se agitó a 50°C durante 3 h. La mezcla de reacción se vertió en agua, y la mezcla se neutralizó con una solución 1 M de ácido clorhídrico (11.1 ml) y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}acrílico (1.79 g, rendimiento: 69%) en forma de cristales incoloros. Punto de fusión 144-146°C.

Ejemplo de referencia 322

A una mezcla de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-3-isopropoxipropoxi)fenil]acrilato de etilo (3.15 g), tetrahidrofurano (10 ml), y etanol (10 ml) se añadió una solución 1 M de hidróxido de sodio (12.5 ml), y la mezcla se agitó a 50°C durante 3 h. La mezcla de reacción se vertió en agua, y la mezcla se neutralizó con una solución 1 M de ácido clorhídrico (12.6 ml) y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-3-

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isopropoxipropoxi)fenil]acrílico (2.18 g, rendimiento: 73%) en forma de cristales incoloros. Punto de fusión 92-93°C.

Ejemplo de referencia 323

Una mezcla de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-3-isopropoxipropoxi)fenil]acrílico (772 mg), piridina (0.014 ml), y anhídrido acético (4 ml) se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v). El aceite obtenido se disolvió en tetrahidrofurano (20 ml), se añadió carbonato ácido de sodio acuoso saturado (10 ml), y la mezcla se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró, Una solución 1 M de ácido clorhídrico se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-(4-[2-(acetiloxi)-3-isopropoxipropoxi]-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrílico (441 mg, rendimiento: 53%) en forma de cristales incoloros. Punto de fusión 134-135°C.

Ejemplo de referencia 324

A una mezcla de 5-metil-1H-pirrol-2-carbaldehído (2.00 g), cloruro de 2,4-diclorobencilo (3.95 g) y N,N-

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dimetilformamida (10 ml) se añadió hidruro de sodio (60% en aceite, 806 mg) a 0°C, y la mezcla se agitó a 0°C durante 1 hora y a temperatura ambiente durante 8 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:10 - 1:4, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar 1-(2,4-diclorobencil)-5-metil-1H-pirrol-2-carbaldehído (4.35 g, rendimiento: 89%) en forma de cristales de color amarillo pálido. Punto de fusión 86-87°C.

Ejemplo de referencia 325

Una mezcla de 1-(2,4-diclorobencil)-5-metil-1H-pirrol-2-carbaldehído (3.76 g), ácido malónico (5.84 g), piperidina (3.46 ml) y piridina (25 ml) se agitó a 110°C durante 8 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró. Se añadió una solución 1 M de ácido clorhídrico al residuo, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[1-(2,4-diclorobencil)-5-metil-1H-pirrol-2-il]acrílico (2.51 g, rendimiento: 58%) en forma de cristales amarillos. Punto de fusión 181-182°C.

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Ejemplo de referencia 326

A una mezcla de 3.5-dimetil-1H-pirrol-2-carbaldehído (3.30 g), cloruro de 2,4-diclorobencilo (5.76 g), y N,N-dimetilformamida (30 ml) se añadió hidruro de sodio (60% en aceite, 1.18 g) a 0°C, y la mezcla se agitó a 0°C durante 1 hora y a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:10 - 1:5, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar 1-(2,4-diclorobencil)-3.5-dimetil-1H-pirrol-2-carbaldehído (5.16 g, rendimiento: 65%) en forma de cristales amarillos. Punto de fusión 88-89°C.

Ejemplo de referencia 327

Una mezcla de 1-(2,4-diclorobencil)-3.5-dimetil-1H-pirrol-2-carbaldehído (5.71 g), ácido malónico (8.41 g), piperidina (4.99 ml) y piridina (30 ml) se agitó a 110°C durante 10 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró. Una solución 1 M de ácido clorhídrico se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se

eluyó con acetato de etilo-hexano (1:5 - 1:1, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[1-(2,4-diclorobencil)-3.5-dimetil-1H-pirrol-2-il]acrílico (914 mg, rendimiento: 14%) en forma de cristales amarillos. Punto de fusión 193-194°C.

Ejemplo de referencia 328

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metoximetoxi)-1.1-dimetilpropoxi]fenil}-N-(pentilsulfonil)acrilamida (111 mg) en acetona (3 ml) se añadió ácido clorhídrico 1 N (2 ml), y la mezcla se agitó a 50°C durante 6 h. Tras dejar enfriar hasta temperatura ambiente, se añadió una solución acuosa saturada de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio hemihidrato de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)-N-(pentilsulfonil)acrilamida (69 mg, rendimiento: 78%) en forma de cristales blancos. Punto de fusión 80-83°C.

Ejemplo de referencia 329

Una mezcla de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)benzaldehído (1.00 g), ácido malónico (280 mg), pirrolidina (0.225 ml) y ácido acético (5 ml) se agitó a 100°C durante 4.5 h, y se enfrió hasta

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temperatura ambiente. Se añadieron sucesivamente ácido clorhídrico 1 N (2 ml) y agua (20 ml) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 hora. Los cristales precipitados se recogieron por filtración, se lavaron dos veces con agua (20 ml) y se secaron al aire. Se añadió éter diisopropílico-hexano (1:1, v/v, 10 ml) al polvo amarillo obtenido, y la mezcla se agitó durante 1 hora. Los cristales se recogieron por filtración, se lavaron tres veces con éter diisopropílico-hexano (1:1, v/v, 10 ml) y se secaron para dar ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (989 mg, rendimiento: 88%) en forma de cristales de color amarillo pálido.

Ejemplo de referencia 330

A una solución de (2E)-3-[2-hidroxi-4-(2-metoxietoxi)fenil]acrilato de etilo (2.50 g) en N,N-dimetilformamida (20 ml) se añadieron 2.5-dibromo-3-metil-6-piridina (3.06 g) y carbonato de potasio (3.24 g), y la mezcla se agitó a 100°C durante 72 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar (2E)-3-[2-[(5-bromo-3-metilpiridin-2-il)oxi]-4-(2-

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metoxietoxi)fenil]acrilato de etilo (2.16 g, rendimiento: 52%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.28 (3 H, t, J = 7.1 Hz), 2.38 (3 H, s), 3.42 (3 H, s), 3.71 - 3.74 (2 H, m), 4.09 - 4.12 (2 H, m), 4.19 (2 H, q, J = 7.1 Hz), 6.33 (1 H, d, J = 16.0 Hz), 6.59 (1 H, d, J = 2.6 Hz), 6.81 (1 H, dd, J = 8.8, 2.6 Hz), 7.60 (1 H, d, J = 8.8 Hz), 7.66 - 7.67 (1 H, m), 7.76 (1 H, d, J = 16.0 Hz), 7.99 (1 H, d, J = 1.9 Hz).

Ejemplo de referencia 331

A una solución mixta de (2E)-3-[2-[(5-bromo-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrilato de etilo (880 mg) en tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4.0 ml), y la mezcla se agitó a 60°C durante 1 hora. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en acetato de etilo-hexano para dar ácido (2E)-3-[2-[(5-bromo-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrílico (785 mg, rendimiento: 95%) en forma de cristales incoloros. Punto de fusión 157.0-157.9°C.

Ejemplo de referencia 332

A una solución de 2-[(3,5-dicloropiridin-2-il)oxi]-

4-(3-metoxipropoxi)benzaldehído (1.50 g) en tetrahidrofurano (15 ml) se añadieron metoxiacetato de metilo (0.97 g) y ter-butóxido de sodio (1.05 g), y la mezcla se agitó a temperatura ambiente durante 24 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2Z)-3-[2-hidroxi-4-(3-metoxipropoxi)fenil]-2-metoxiacrilato de metilo (870 mg, rendimiento: 69%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:2.00 - 2.05 (2 H, m), 3.35 (3 H, s), 3.54 (2 H, t, J = 6.1 Hz), 3.78 (3 H, s), 3.86 (3 H, s), 4.06 (2 H, t, J = 6.1 Hz), 6.45 - 6.48 (2 H, m), 7.09 (1 H, d, J = 9.6 Hz), 7.14 (1 H, s), 9.08 (1 H, s).

Ejemplo de referencia 333

A una solución de (2Z)-3-[2-hidroxi-4-(3-metoxipropoxi)fenil]-2-metoxiacrilato de metilo (836 mg) en N,N-dimetilformamida (8 ml) se añadieron 2.3-dicloro-5-(trifluorometil)piridina (920 mg) y carbonato de potasio (780 mg), y la mezcla se agitó a 80°C durante 5 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de

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sílice, y se eluyó con acetato de etilo- hexano (1:4, v/v) para dar (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-2-metoxiacrilato de metilo (1.25 g, rendimiento: 93%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:2.00 - 2.05 (2 H, m), 3.34 (3 H, s), 3.53 (2 H, t, J = 6.0 Hz), 3.73 (3 H, s), 3.77 (3 H, s), 4.07 (2 H, t, J = 6.0 Hz), 6.68 (1 H, s), 6.88 (1 H, dd, J = 8.9, 2.6 Hz), 7.04 (1 H, s), 8.00 (1 H, d, J = 2.6 Hz), 8.22 (1 H, d, J = 8.9 Hz), 8.25 - 8.26 (1 H, m).

Ejemplo de referencia 334

A una solución mixta de (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-2-metoxiacrilato de metilo (1.07 g) en tetrahidrofurano (4 ml) y metanol (4 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4.5 ml), y la mezcla se agitó a 60°C durante 1 hora. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar ácido (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-2-metoxiacrílico (582 mg,

rendimiento: 56%) en forma de cristales incoloros. Punto de fusión 153.0-153.5°C.

Ejemplo de referencia 335

A una solución de 3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]propanoato de etilo (4.84 g) en tolueno (50 ml) se añadió una solución de hidruro de diisobutilaluminio 1.5 M en tolueno (16.0 ml) a 0°C, y la mezcla se agitó a 0°C durante 5 h. Se añadieron metanol y celite a la mezcla de reacción, y la mezcla se agitó durante 30 min. Se filtró el celite, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3, v/v) para dar 3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]propan-1-ol (3.35 g, rendimiento: 78%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.54 (1 H, s), 1.78 - 1.86 (2 H, m), 2.69 (2 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.54 - 3.60 (2 H, m), 3.71 - 3.74 (2 H, m), 4.07 - 4.10 (2 H, m), 5.02 (2 H, s), 6.46 (1 H, dd, J = 8.3, 2.3 Hz), 6.58 (1 H, d, J = 2.3 Hz), 7.05 (1 H, d, J = 8.3 Hz), 7.30 - 7.50 (5 H, m).

Ejemplo de referencia 336

A una solución de 3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]propan-1-ol (1.01 g) en tetrahidrofurano (15 ml) se añadió N,N'-carbonildiimidazol (780 mg), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió (aminometil)ciclopropano (475 mg) a la mezcla de reacción, y

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la mezcla se agitó a temperatura ambiente durante 5 h. La mezcla de reacción se concentró, el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7, v/v) para dar (ciclopropilmetil)carbamato de 3-[2-(benciloxi)-4-(2-metoxietoxi)fenil]propilo en forma de un sólido amorfo incoloro(1.20 g). El sólido amorfo obtenido se disolvió en metanol (100 ml), se añadió paladio sobre carbón al 10% (130 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar (ciclopropilmetil)carbamato de 3-[2-hidroxi-4-(2-metoxietoxi)fenil]propilo (940 mg, rendimiento: 99%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.16 - 0.22 (2 H, m), 0.48 - 0.53 (2 H, m), 0.91 - 0.99 (1 H, m), 1.86 - 1.95 (2 H, m), 2.61 (2 H, t, J = 7.3 Hz), 3.02 - 3.07 (2 H, m), 3.44 (3 H, s), 3.71 - 3.74 (2 H, m), 4.05 - 4.11 (4 H, m), 4.76 - 4.83 (1 H, m), 5.59 (1 H, s), 6.41 - 6.46 (2 H, m), 6.97 (1 H, d, J = 8.1 Hz).

Ejemplo de referencia 337

Bajo enfriamiento con hielo, a una mezcla de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-

(metoximetoxi)benzaldehído (10.0 g), 2-fosfonopropionato de trietilo (7.24 g), tetrahidrofurano (30 ml) y N,N-dimetilformamida (30 ml) se añadió hidróxido de litio monohidratado (1.28 g), y la mezcla se agitó durante 2 h. Se añadió ácido clorhídrico 0.1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar una mezcla (11.4 g) de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]-2-metilacrilato de etilo y (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]-2-metilacrilato de etilo.

A una solución de la mezcla obtenida (5.00 g) en etanol (50 ml) se añadió ácido clorhídrico concentrado (2.5 ml), y la mezcla se agitó a 50°C durante 5 h. La mezcla de reacción se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)-2-metilacrilato de etilo (3.04 g, 73%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.26 (3 H, t, J = 7.2 Hz), 2.01 (3 H, d, J = 1.5 Hz), 4.17 (2 H, q, J = 7.0 Hz), 5.11 (1 H, s), 6.72 (1 H, d, J = 2.4 Hz), 6.80 (1 H, dd, J = 8.5, 2.4 Hz), 7.35 (1 H, d, J = 8.5 Hz), 7.50 (1 H, d, J = 1.3 Hz), 7.97 (1 H, d, J = 2.3 Hz), 8.24 (1 H, dd, J = 2.1, 1.1 Hz).

Ejemplo de referencia 338

A una solución de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)-2-metilacrilato de etilo (3.00 g) en N,N-dimetilformamida (50 ml) se añadieron isopropilyoduro (1.50 ml) y carbonato de potasio (4.12 g), y la mezcla se agitó a 50°C durante 2 h. La mezcla de reacción se filtró, se añadió acetato de etilo al filtrado. La mezcla se lavó sucesivamente con salmuera saturada y agua, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 2:8, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrilato de etilo (3.17 g, 96%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.25 (3 H, t, J = 7.1 Hz), 1.36 (6 H, d, J = 6.0 Hz), 1.96 - 2.09 (3 H, m), 4.02 - 4.27 (2 H, m), 4.42 - 4.67 (1 H, m), 6.72 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.6, 2.4 Hz), 7.39 (1 H, d, J = 8.7 Hz), 7.51 (1 H, s), 7.96 (1 H, d, J = 2.1 Hz), 8.23 (1 H, d, J =

0.9 Hz).

Ejemplo de referencia 339

A una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrilato de etilo (3.00 g), etanol (20 ml), tetrahidrofurano (10 ml) y agua (10 ml) se añadió hidróxido de litio monohidratado (2.27 g), y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se acidificó con ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 2:8, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (2.00 g, 71%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.36 (6 H, d, J = 6.0 Hz), 2.05 (3 H, d, J = 1.5 Hz), 4.48 - 4.64 (1 H, m), 6.70 (1 H, d, J = 2.4 Hz), 6.85 (1 H, dd, J = 8.7, 2.4 Hz), 7.41 (1 H, d, J = 8.7 Hz), 7.64 (1 H, s), 7.97 (1 H, d, J = 1.9 Hz), 8.19 - 8.28 (1 H, m).

Ejemplo de referencia 340

A una solución de alcohol bencílico (2.00 g) en acetonitrilo (100 ml) se añadió clorosulfonilisocianato (2.75

g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (5.3 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-(aminoetil)-5-metilpirazina (11.4 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:8 - 1:0, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({[(5-metilpirazin-2-il)metil]amino}sulfonil)carbamato de bencilo (3.27 g, 53%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:2.55 (3 H, s), 4.38 - 4.49 (2 H, m), 5.15 (2 H, s), 6.06 (1 H, br.s.), 7.32 - 7.47 (6 H, m), 8.30 (1 H, s), 8.46 (1 H, s).

Ejemplo de referencia 341

A una solución de alcohol bencílico (2.00 g) en acetonitrilo (100 ml) se añadió clorosulfonilisocianato (2.75 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (5.3 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora, se agregó 2-(2-aminoetil)piridina (11.3 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió

ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con metanol-acetato de etilo (0:1 - 1:0, v/v) y se concentró para dar {[(2-piridin-2-iletil)amino]sulfonil}carbamato de bencilo (4.58 g, 74%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:3.03 (2 H, t, J = 6.3 Hz), 3.44 - 3.55 (2 H, m), 5.12 (2 H, s), 7.08 - 7.18 (2 H, m), 7.32 (5 H, s), 7.55 - 7.66 (1 H, s), 8.40 - 8.48 (1 H, m).

Ejemplo de referencia 342

A una solución de alcohol bencílico (2.00 g) en acetonitrilo (100 ml) se añadió clorosulfonilisocianato (2.75 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (5.3 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora, se agregó 2-(2-aminoetil)piridina (11.3 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano

para dar (pirrolidin-1-ilsulfonil)carbamato de bencilo (2.99 g, 54%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.80 - 1.96 (4 H, m), 3.41 - 3.54 (4 H, m), 5.17 (2 H, s), 7.16 (1 H, br.s.), 7.32 - 7.43 (5 H, s).

Ejemplo de referencia 343

Una suspensión de ({[(5-metilpirazin-2-il)metil]amino}sulfonil)carbamato de bencilo (3.00 g) y paladio sobre carbón al 10% (0.30 g) en metanol (80 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h. La mezcla de reacción se filtró, y el solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con metanol-acetato de etilo (0:1 - 2:8, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar N-[(5-metilpirazin-2-il)metil]sulfamida (1.29 g, 72%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:2.59 (3 H, s), 4.47 (2 H, s), 4.68 (2 H, br.s.), 5.33 (1 H, br.s.), 8.41 (1 H, s), 8.50 (1 H, s).

Ejemplo de referencia 344

Una suspensión de {[(2-piridin-2-iletil)amino]sulfonil}carbamato de bencilo (4.58 g) y paladio sobre carbón al 10% (0.46 g) en etanol (100 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h.

La mezcla de reacción se filtró, y el solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con metanol-acetato de etilo (0:1 - 1:0, v/v) y se concentró para dar N-(2-piridin-2-iletil)sulfamida (1.46 g, 53%) en forma de un sólido incoloro.

^{1}H-RMN (300 MHz, DMSO-d_6) δ: 2.94 (2 H, t, J = 7.6 Hz), 3.16 - 3.29 (2 H, m), 6.41 - 6.69 (3 H, m), 7.13 - 7.34 (2 H, m), 7.62 - 7.78 (1 H, m), 8.49 (1 H, d, J = 4.5 Hz).

Ejemplo de referencia 345

Una suspensión de (pirrolidin-1-ilsulfonil)carbamato de bencilo (2.50 g) y paladio sobre carbón al 10% (0.30 g) en etanol (80 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h. La mezcla de reacción se filtró, y el solvente se evaporó a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar pirrolidin-1-sulfonamida (1.04 g, 79%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.81 - 2.02 (4 H, m), 3.19 - 3.37 (4 H, m), 4.50 (2 H, br.s.).

Ejemplo de referencia 346

Una mezcla de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)acrilato de etilo (11.4 g), óxido de platino (IV) (133 mg) y etanol-tetrahidrofurano (292 ml, v/v=1/1) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h. El

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catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (10.8 g, rendimiento: 94%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.14 - 1.31 (3 H, m), 2.57 (2 H, t, J = 7.6 Hz), 2.75 (2 H, t, J = 7.7 Hz), 4.02 - 4.18 (2 H, m), 5.48 (1 H, d, J = 7.0 Hz), 6.59 (1 H, d, J = 2.4 Hz), 6.68 (1 H, dd, J = 8.3, 2.4 Hz), 7.17 (1 H, d, J = 8.3 Hz), 7.99 (1 H, s), 8.27 (1 H, s).

Ejemplo de referencia 347

A una mezcla de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (1.01 g), 1-butanol (0.29 g), tributilfosfina (1.05 g) y tetrahidrofurano (10 ml) se añadió 1,1'-(azodicarbonil)dipiperidina (1.31 g) a temperatura ambiente, y la mezcla se agitó durante 30 min. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:9 - 3:7, v/v) para dar 3-(4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propanoato de etilo (1.1 g, rendimiento: 95%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.96 (3 H, t, J = 7.4 Hz), 1.21 (3 H, t, J = 7.2 Hz), 1.37 - 1.81 (4 H, m), 2.52 - 2.61 (2 H, m), 2.70 - 2.80 (2 H, m), 3.87 - 3.97 (2 H, m), 4.03 - 4.15 (2 H, m), 6.64 (1 H, d, J = 2.6 Hz), 6.78 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.27 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 348

Se disolvió 3-(4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propanoato de etilo (1.1 g) en éter dietílico (5 ml), se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (4.1 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 1.5 h. Se añadieron metanol y agua a la mezcla de reacción, y la mezcla se agitó durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 2:3, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio 3-(4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propan-1-ol (0.69 g, rendimiento: 69%) en forma de cristales incoloros. Punto de fusión 72.6-72.7°C.

Ejemplo de referencia 349

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (1.03 g) en N,N-dimetilformamida (5.3 ml) se añadieron

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1-bromo-3-metoxipropano (0.60 g), carbonato de potasio (0.73 g) y yoduro de sodio (0.80 g), y la mezcla se agitó a 80°C durante 18 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:17 - 2:3, v/v) para dar un 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propanoato de etilo (0.84 g, rendimiento: 69%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.0 Hz), 1.98 - 2.08 (2 H, m), 2.56 (2 H, t, J = 7.8 Hz), 2.76 (2 H, t, J = 7.6 Hz), 3.34 (3 H, s), 3.53 (2 H, t, J = 6.1 Hz), 3.96 - 4.14 (4 H, m), 6.65 (1 H, d, J = 2.7 Hz), 6.79 (1 H, dd, J = 8.5, 2.5 Hz), 7.22 (1 H, d, J = 8.3 Hz), 7.98 (1 H, d, J = 2.3 Hz), 8.27 (1 H, s).

Ejemplo de referencia 350

Se disolvió 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propanoato de etilo (840 mg) en éter dietílico (3.6 ml), se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (3.0 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadieron metanol y agua a la mezcla de reacción, y la mezcla se agitó

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durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 1:1, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propan-1-ol (665 mg, rendimiento: 87%) en forma de cristales incoloros. Punto de fusión 68.7-70.9°C.

Ejemplo de referencia 351

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (1.03 g) en N,N-dimetilformamida (5.3 ml) se añadió hidruro de sodio (60% en aceite, 0.15 g), y la mezcla se agitó a 0°C durante 30 min. Luego, se añadió 4-bromo-1-buteno (0.53 g), y la mezcla se agitó a 50°C durante 48 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:7, v/v) para dar un 3-(4-(but-3-en-1-iloxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propanoato de etilo (0.68 g, rendimiento: 58%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.1 Hz), 2.47 - 2.61 (4 H, m), 2.76 (2 H, t, J = 7.6 Hz), 3.95 - 4.01

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(2 H, m), 4.04 - 4.13 (2 H, m), 5.06 - 5.20 (2 H, m), 5.80 - 5.96 (1 H, m), 6.65 (1 H, d, J = 2.6 Hz), 6.79 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.27 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 352

Se disolvió 3-(4-(but-3-en-1-iloxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propanoato de etilo (683 mg) en éter dietílico (3.0 ml), se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (2.6 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadieron metanol y agua a la mezcla de reacción, y la mezcla se agitó durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 2:3, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio 3-(4-(but-3-en-1-iloxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propan-1-ol (525 mg, rendimiento: 85%) en forma de cristales incoloros. Punto de fusión 75.2-75.8°C.

Ejemplo de referencia 353

A una mezcla de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (1.09 g), 2-furilmetanol (0.41 g), tributilfosfina (1.14 g) y tetrahidrofurano (11 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.42 g) a temperatura ambiente, y

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la mezcla se agitó durante 30 min. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-furilmetoxi)fenil]propanoato de etilo (1.05 g, rendimiento: 80%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.17 - 1.24 (3 H, m), 2.53 - 2.62 (2 H, m), 2.78 (2 H, t, J = 7.6 Hz), 4.04 - 4.15 (2 H, m), 4.96 (2 H, s), 6.35 - 6.43 (2 H, m), 6.74 (1 H, d, J = 2.6 Hz), 6.87 (1 H, dd, J = 8.5, 2.6 Hz), 7.21 - 7.27 (1 H, m), 7.41 - 7.46 (1 H, m), 7.99 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.3, 0.9 Hz).

Ejemplo de referencia 354

Se disolvió 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-furilmetoxi)fenil]propanoato de etilo (1050 mg) en éter dietílico (4.5 ml), se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (3.7 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadieron metanol y agua a la mezcla de reacción, y la mezcla se agitó durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 2:3, v/v) para dar cristales incoloros. La

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recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-furilmetoxi)fenil]propan-1-ol (734 mg, rendimiento: 77%) en forma de cristales incoloros. Punto de fusión 68.0-68.6°C.

Ejemplo de referencia 355

A una mezcla de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (1.09 g), 4-(2-hidroxietil)morfolina (0.55 g), tributilfosfina (1.13 g) y tetrahidrofurano (11 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.41 g) a temperatura ambiente, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:1 - 7:3, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-morfolin-4-iletoxi)fenil}propanoato de etilo (1.14 g, rendimiento: 81%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.17 - 1.30 (3 H, m), 2.52 - 2.61 (6 H, m), 2.72 - 2.82 (4 H, m), 3.69 - 3.75 (4 H, m), 4.04 - 4.16 (4 H, m), 6.67 (1 H, d, J = 2.6 Hz), 6.79 (1 H, dd, J = 8.5, 2.6 Hz), 7.23 (1 H, d, J = 8.5 Hz), 7.99 (1 H, d, J = 2.3 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo de referencia 356

Se disolvió 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-morfolin-4-

iletoxi)fenil]propanoato de etilo (1139 mg) en éter dietílico (4.5 ml), se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (3.8 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadieron metanol y agua a la mezcla de reacción, y la mezcla se agitó durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-morfolin-4-iletoxi)fenil]propan-1-ol (737 mg, rendimiento: 71%) en forma de cristales incoloros. Punto de fusión 69.2-70.4°C.

Ejemplo de referencia 357

A una mezcla de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propanoato de etilo (1.05 g), alcohol tetrahidrofurfurílico (0.41 g), tributilfosfina (1.09 g) y tetrahidrofurano (10 ml) se añadió 1.1'-(azodicarbonil)dipiperidina (1.36 g) a temperatura ambiente, y la mezcla se agitó durante 20 h. La mezcla de reacción se concentró, se añadió éter diisopropílico, y los cristales precipitados se filtraron. El filtrado se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (3:17 - 1:4, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-

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il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]propanoato de etilo (789 mg, rendimiento: 62%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.21 (3 H, t, J = 7.2 Hz), 1.86 - 2.17 (4 H, m), 2.52 - 2.61 (2 H, m), 2.76 (2 H, t, J = 7.7 Hz), 3.75 - 3.96 (4 H, m), 4.04 - 4.14 (2 H, m), 4.22 - 4.30 (1 H, m), 6.68 (1 H, d, J = 2.6 Hz), 6.81 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo de referencia 358

Se disolvió 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]propanoato de etilo (739 mg) en éter dietílico (3.0 ml), se añadió una solución toluénica 1.5 M de hidruro de diisobutilaluminio (2.6 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadieron metanol y agua a la mezcla de reacción, y la mezcla se agitó durante un tiempo, se filtró a través de celite y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 2:3, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]propan-1-ol (495 mg, rendimiento: 73%) en forma de cristales incoloros. Punto de fusión 91.3-93.6°C.

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Ejemplo de referencia 359

Una suspensión de (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)acrilato de etilo (12.1 g) y paladio sobre carbón al 10% (1.21 g) en etanol (250 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h. La mezcla de reacción se filtró, y el solvente se evaporó a presión reducida para dar 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)propanoato de etilo (12.1 g, cuant.) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.00 - 1.10 (21 H, m), 1.21 (3 H, t, J = 7.2 Hz), 2.47 - 2.64 (2 H, m), 2.76 (2 H, t, J = 7.8 Hz), 3.86 - 4.21 (6 H, m), 6.67 (1 H, d, J = 2.6 Hz), 6.76 - 6.87 (1 H, m), 7.22 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 2.1 Hz), 8.26 (1 H, d, J = 1.1 Hz).

Ejemplo de referencia 360

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)propanoato de etilo (12.1 g) en éter dietílico (50 ml) se añadió gota a gota una solución toluénica 1.5 M de hidruro de diisobutilaluminio (34.3 ml), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 4 h. Se añadió salmuera saturada a la mezcla de reacción, la mezcla se filtró, y el filtrado se

extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 2:8, v/v) y se concentró para dar 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)propan-1-ol (8.74 g, 77%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.98 - 1.19 (21 H, m), 1.37 (1 H, t, J = 5.7 Hz), 1.73 - 1.92 (2 H, m), 2.49 - 2.57 (2 H, m), 3.60 (2 H, q, J = 6.2 Hz), 4.01 - 4.04 (4 H, m), 6.66 (1 H, d, J = 2.4 Hz), 6.77 - 6.88 (1 H, m), 7.22 (1 H, d, J = 8.7 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo 1

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (3.49 g) en tetrahidrofurano (40 ml) se añadió N,N'-carbonildiimidazol (2.08 g), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (1.63 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (2.0 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N,

una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (1.62 g, rendimiento: 35%) en forma de cristales en pluma blancos. Punto de fusión 140-142°C.

Ejemplo 2

A una solución de ácido 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propiónico (530 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (313 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (225 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en

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acetato de etilo-hexano dio 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-(pentilsulfonil)propanamida (353 mg, rendimiento: 50%) en forma de cristales en pluma blancos. Punto de fusión 94-95°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.85 - 0.94 (3 H, m), 1.24 - 1.41 (10 H, m), 1.60 - 1.73 (2 H, m), 2.55 (2 H, t, J = 7.2 Hz), 2.96 (2 H, t, J = 7.1 Hz), 3.12 - 3.20 (2 H, m), 4.36 - 4.55 (1 H, m), 6.45 (1 H, d, J = 2.4 Hz), 6.74 (1 H, dd, J = 8.4, 2.5 Hz), 7.17 (1 H, d, J = 8.5 Hz), 8.08 (1 H, d, J = 2.1 Hz), 8.33 - 8.43 (1 H, m).

La recristalización de los cristales crudos obtenidos en las mismas condiciones que en el Ejemplo 2 a partir de acetato de etilo-hexano dio cristales. El patrón de difracción de polvos por rayos X de este cristal tal como se midió usando rayo de Cu-Kα (voltaje del tubo: 40 KV; corriente del tubo: 50 mA) como una fuente de radiación y RINT2100 tipo Ultima+ (Rigaku Corporation) se muestra en la Fig. 1.

Datos (pico principal) de la difracción de polvos por rayos X

Ángulo de difracción: 2θ (°)	Espaciado: valor d (angstrom))
6.50	13.6
12.8	6.90
16.4	5.39
17.2	5.15
19.5	4.54

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22.1	4.01
22.7	3.91
24.2	3.67

Ejemplo 3

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (502 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (213 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron bencensulfonamida (212 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.25 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:4, v/v) para dar un aceite incoloro. Se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-metanol (acetato de etilo solo a 4:1, v/v) y luego con solución metanólica 2.0 M de amoníaco para dar un aceite amarillo. El aceite obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar 3-[2-{[3-

cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(fenilsulfonil)propanamida (338 mg, rendimiento: 51%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.46 (2 H, t, J = 7.2 Hz), 2.84 (2 H, t, J = 7.1 Hz), 3.44 (3 H, s), 3.73 (2 H, dd, J = 5.4, 3.9 Hz), 4.04 (2 H, dd, J = 5.4, 3.9 Hz), 6.33 - 6.46 (2 H, m), 6.78 (1 H, d, J = 8.5 Hz), 7.44 - 7.55 (1 H, m), 7.60 - 7.69 (1 H, m), 7.82 - 7.89 (2 H, m), 8.08 (1 H, d, J = 1.9 Hz), 8.42 - 8.51 (1 H, m), 9.39 (1 H, s).

Ejemplo 4

A una solución de ácido 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propiónico (1.47 g) en tetrahidrofurano (20 ml) se añadieron cloruro de tionilo (0.75 ml) y N,N-dimetilformamida (0.10 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (20 ml). Se añadieron bencensulfonamida (685 mg), N,N-diisopropiletilamina (0.80 ml) y 4-dimetilaminopiridina (431 mg) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó durante 3 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se

eluyó con acetato de etilo-hexano (1:9 - 3:2, v/v) para dar un aceite de color amarillo pálido. Esto se disolvió en una suspensión de carbón activado en acetato de etilo, la mezcla se agitó a temperatura ambiente durante 30 min, se filtró y se concentró para dar un sólido de color amarillo pálido. La recristalización en acetato de etilo-hexano dio 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-(fenilsulfonil)propanamida (1.02 g, rendimiento: 52%) en forma de cristales blancos. Punto de fusión 129.0-129.5°C.

Ejemplo 5

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (114 mg) en tetrahidrofurano (2 ml) se añadieron cloruro de tionilo (0.05 ml) y N,N-dimetilformamida (0.01 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (2 ml). Se agregaron 4-clorobencensulfonamida (60 mg), N,N-diisopropiletilamina (0.05 ml) y 4-dimetilaminopiridina (39 mg) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó durante 3 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en

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columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar una N-[(4-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanamida (88 mg, rendimiento: 54%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 140-141.5°C.

Ejemplo 6

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (140 mg) en tetrahidrofurano (2 ml) se añadieron cloruro de tionilo (0.05 ml) y N,N-dimetilformamida (0.01 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (2 ml). Se añadieron p-toluensulfonamida (65 mg), N,N-diisopropiletilamina (0.10 ml) y 4-dimetilaminopiridina (42 mg) a la mezcla de reacción a temperatura ambiente, y 30 min más tarde, se agregó N,N-diisopropiletilamina (0.10 ml). Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar un

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aceite de color amarillo pálido. El aceite obtenido se mezcló con una cantidad en exceso de trietilamina, y una cantidad en exceso del reactivo se evaporó a presión reducida. La mezcla obtenida se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 4:1, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(4-metilfenil)sulfonil]propanamida (23 mg, 12%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.42 - 2.51 (2 H, m), 2.83 (2 H, t, J = 7.3 Hz), 3.44 (3 H, s), 3.70 - 3.77 (2 H, m), 4.00 - 4.11 (2 H, m), 6.40 - 6.49 (2 H, m), 6.82 (1 H, d, J = 9.1 Hz), 7.22 - 7.35 (2 H, m), 7.72 (2 H, d, J = 8.5 Hz), 8.06 (1 H, d, J = 2.2 Hz), 8.42 (1 H, s).

Ejemplo 7

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (169 mg) en tetrahidrofurano (2 ml) se añadieron cloruro de tionilo (0.05 ml) y N,N-dimetilformamida (0.01 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (2 ml). Se agregaron 4-metoxibencensulfonamida (85 mg), N,N-diisopropiletilamina (0.10 ml) y 4-dimetilaminopiridina (62 mg) a la mezcla de reacción a temperatura ambiente, y la

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mezcla se agitó durante 80 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar un aceite incoloro. Esto se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-metanol (acetato de etilo solo a 4:1, v/v), luego con una solución metanólica 2.0 M de amoníaco para dar un sólido rojo. El sólido obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(4-metoxifenil)sulfonil]propanamida (125 mg, rendimiento: 53%) en forma de un sólido incoloro. La recristalización en acetato de etilo-hexano dio un polvo blanco. Punto de fusión 118-120°C.

Ejemplo 8

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (494 mg) en tetrahidrofurano (5 ml) se añadieron cloruro de tionilo (0.15 ml) y N,N-dimetilformamida (0.05 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se

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concentró, y el residuo se disolvió en tetrahidrofurano (5 ml). Se añadieron 2-clorobencensulfonamida (245 mg), N,N-diisopropiletilamina (0.40 ml) y 4-dimetilaminopiridina (167 mg) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 1:1, v/v) para dar un aceite incoloro. El aceite obtenido se mezcló con una cantidad en exceso de trietilamina, y una cantidad en exceso del reactivo se evaporó a presión reducida. La mezcla obtenida se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 4:1, v/v) para dar N-[(2-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanamida (608 mg, 87%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.55 (2 H, t, J = 7.3 Hz), 2.78 (2 H, t, J = 7.3 Hz), 3.43 (3 H, s), 3.70 - 3.76 (2 H, m), 4.01 - 4.10 (2 H, m), 6.56 (1 H, d, J = 2.5 Hz), 6.68 (1 H, dd, J = 8.5, 2.5 Hz), 7.03 (1 H, d, J = 8.5 Hz), 7.38 - 7.48 (2 H, m), 7.49 - 7.59 (1 H, m), 8.00 (1 H, d, J = 2.2 Hz), 8.20 (1 H, dd, J = 7.8, 1.8 Hz), 8.33 (1 H, d, J = 1.4 Hz).

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Ejemplo 9

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (515 mg) en tetrahidrofurano (5 ml) se añadieron cloruro de tionilo (0.15 ml) y N,N-dimetilformamida (0.05 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (5 ml). Se añadieron o-toluensulfonamida (221 mg), N,N-diisopropiletilamina (0.40 ml) y 4-dimetilaminopiridina (140 mg) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 1:1, v/v) para dar una 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(2-metilfenil)sulfonil]propanamida (171 mg, rendimiento: 24%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.37 (3 H, s), 2.50 (2 H, t, J = 7.2 Hz), 2.82 (2 H, t, J = 7.2 Hz), 3.44 (3 H, s), 3.68 - 3.79 (2 H, m), 4.03 - 4.10 (2 H, m), 6.45 - 6.62 (2 H, m), 6.88 (1 H, d, J = 8.5 Hz), 7.22 - 7.27 (1 H, m), 7.30 - 7.39

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(1 H, m), 7.44 - 7.57 (1 H, m), 7.97 - 8.11 (2 H, m), 8.42 (1 H, d, J = 1.1 Hz), 9.19 (1 H, s).

Ejemplo 10

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (498 mg) en tetrahidrofurano (5 ml) se añadieron cloruro de tionilo (0.15 ml) y N,N-dimetilformamida (0.05 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 3 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (5 ml). Se añadieron 4-etilbencensulfonamida (249 mg), N,N-diisopropiletilamina (0.40 ml) y 4-dimetilaminopiridina (158 mg) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 1:1, v/v) para dar una 3-[2-{{3-cloro-5-(trifluorometil)piridin-2-il}oxi}-4-(2-metoxietoxi)fenil]-N-[(4-etilfenil)sulfonil]propanamida (157 mg, rendimiento: 23%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.29 (3 H, t, J = 7.7 Hz), 2.45 (2 H, t, J = 7.1 Hz), 2.69 - 2.89 (4 H, m), 3.44 (3 H,

s), 3.70 - 3.76 (2 H, m), 4.02 - 4.07 (2 H, m), 6.39 - 6.52 (2 H, m), 6.82 (1 H, d, J = 8.0 Hz), 7.28 - 7.36 (2 H, m), 7.70 - 7.81 (2 H, m), 8.06 (1 H, d, J = 2.2 Hz), 8.37 - 8.49 (1 H, m), 9.21 (1 H, s).

Ejemplo 11

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (496 mg) en tetrahidrofurano (5 ml) se añadieron cloruro de tionilo (0.15 ml) y N,N-dimetilformamida (0.05 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 2 h. La mezcla de reacción se concentró, y el residuo se disolvió en tetrahidrofurano (5 ml). Se añadieron 4-fluorobencensulfonamida (225 mg), N,N-diisopropiletilamina (0.40 ml) y 4-dimetilaminopiridina (140 mg) a la mezcla de reacción a temperatura ambiente, y la mezcla se agitó durante la noche. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 1:1, v/v) para dar un sólido blanco. El sólido obtenido se mezcló con una cantidad en exceso de trietilamina, y una cantidad en exceso del reactivo se evaporó a presión reducida. La mezcla obtenida se sometió a cromatografía en

columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1 - 9:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(4-fluorofenil)sulfonil]propanamida (105 mg, rendimiento: 15%) en forma de un polvo blanco. Punto de fusión 136-138°C.

Ejemplo 12

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (2.31 g) en tetrahidrofurano (50 ml) se añadió N,N'-carbonildiimidazol (1.37 g), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (1.02 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.80 ml) a la mezcla de reacción, y la mezcla se agitó durante 3 h. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-

(pentilsulfonil)acrilamida (493 mg, rendimiento: 16%) en forma de cristales blancos. Punto de fusión 127-130°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.89 (3 H, t, J = 7.1 Hz), 1.24 - 1.48 (4 H, m), 1.83 (2 H, tt, J = 7.6, 7.6 Hz), 3.44 (3 H, s), 3.45 - 3.50 (2 H, m), 3.71 - 3.80 (2 H, m), 4.04 - 4.20 (2 H, m), 6.37 (1 H, d, J = 15.6 Hz), 6.70 (1 H, d, J = 2.4 Hz), 6.91 (1 H, dd, J = 8.7, 2.4 Hz), 7.60 (1 H, d, J = 8.9 Hz), 7.79 (1 H, d, J = 15.6 Hz), 7.87 (1 H, s), 8.03 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.2, 1.0 Hz).

La recristalización de los cristales crudos obtenidos en las mismas condiciones que en el Ejemplo 12 de etanol dio cristales. El patrón de difracción de polvos por rayos X de este cristal tal como se midió usando rayo de Cu-Kα (voltaje del tubo: 40 KV; corriente del tubo: 50 mA) como una fuente de radiación y RINT2100 tipo Ultima+ (Rigaku Corporation) se muestra en la Fig. 2.

Datos (pico principal) de la difracción de polvos por rayos X

Ángulo de difracción: 2θ (°)	Espaciado: valor d (angstrom)
7.18	12.3
14.2	6.27
16.3	5.44
17.8	4.99
18.7	4.74
21.7	4.09

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23.3	3.81
25.7	3.46
27.0	3.29

Ejemplo 13

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]acrílico (0.95 g) en tetrahidrofurano (20 ml) se añadió N,N'-carbonildiimidazol (628 mg), y la mezcla se calentó a reflujo durante 1.5 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (397 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.50 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]-N-(pentilsulfonil)acrilamida (438 mg, rendimiento: 35%) en forma de agujas finas blancas. Punto de fusión 142-144°C.

Ejemplo 14

A una solución de 3-[2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (79 mg) en acetonitrilo (5 ml) se añadió bencensulfonilisocianato (105 mg), y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 3:2, v/v) para dar un sólido blanco. El sólido se recristalizó en acetato de etilo-hexano y el sólido obtenido se lavó con acetonitrilo, se sometió a cromatografía en columna con gel de sílice básica y se eluyó con solución metanólica 2.0 M de amoníaco para dar un sólido rojo. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar una N-[({3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}amino)carbonil] bencensulfonamida (15 mg, rendimiento: 13%, pureza del 90%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.67 - 1.86 (2 H, m), 2.43 (2 H, t, J = 7.6 Hz), 3.19 (2 H, d, J = 6.0 Hz), 3.43 (3 H, s), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.09 (2 H, dd, J = 5.4, 3.9 Hz), 6.57 (1 H, t, J = 5.6 Hz), 6.67 (1 H, t, J = 2.6 Hz), 6.81 (1 H, dd, J = 8.5, 2.6 Hz), 7.13 (1 H, d, J = 8.5 Hz), 7.40 - 7.53 (2 H, m), 7.60 (1 H, t, J = 7.5 Hz), 7.78 - 7.93 (2 H, m), 7.99 (1 H, d, J = 1.9 Hz), 8.25 (1 H, dd, J = 2.2,

1.0 Hz).

Ejemplo 15

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (492 mg) en acetato de etilo (20 ml) se añadieron trietilamina (0.20 ml) y cloruro de metansulfonilo (0.25 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido de color anaranjado pálido. La recristalización en acetato de etilo-hexano dio N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}metansulfonamida (211 mg, rendimiento: 36%) en forma de cristales blancos. Punto de fusión 89-90°C.

Ejemplo 16

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (455 mg) en acetato de etilo (10 ml) se añadieron piridina (1.0 ml) y cloruro de

bencensulfonilo (0.15 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido incoloro. La recristalización en acetato de etilo-hexano dio N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}bencensulfonamida (205 mg, rendimiento: 34%) en forma de cristales blancos. Punto de fusión 94-95°C.

Ejemplo 17

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (451.1 mg) en acetato de etilo (10 ml) se añadieron piridina (1.0 ml) y 2,4-diclorocloruro de bencensulfonilo (301 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera

saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido de color amarillo pálido. El sólido obtenido se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar 2,4-dicloro-N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}bencensulfonamida (236 mg, rendimiento: 35%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.68 - 1.82 (2 H, m), 2.46 (2 H, t, J = 7.3 Hz), 2.75 - 2.96 (2 H, m), 3.44 (3 H, s), 3.65 - 3.78 (2 H, m), 4.00 - 4.15 (2 H, m), 4.99 (2 H, t, J = 6.1 Hz), 6.65 (1 H, d, J = 2.4 Hz), 6.80 (1 H, dd, J = 8.5, 2.4 Hz), 7.11 (1 H, d, J = 8.5 Hz), 7.37 (1 H, dd, J = 8.5, 1.9 Hz), 7.51 (1 H, d, J = 1.9 Hz), 7.90 - 8.03 (2 H, m), 8.25 (1 H, d, J = 0.9 Hz).

Ejemplo 18

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (1.01 g) en acetato de etilo (10 ml) se añadieron piridina (2.5 ml) y cloruro de 1-pentansulfonilo (0.50 g), y la mezcla se agitó a temperatura ambiente durante 1.5 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la

mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}pentan-1-sulfonamida (198 mg, rendimiento: 15%) en forma de cristales blancos. Punto de fusión 87-90°C.

Ejemplo 19

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (289 mg) en acetato de etilo (10 ml) se añadieron piridina (5.0 ml) y cloruro de fenilmetansulfonilo (182.1 mg), y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La

recristalización en acetato de etilo-hexano dio N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}-1-fenilmetansulfonamida (75 mg, rendimiento: 19%) en forma de cristales blancos. Punto de fusión 97-100°C.

Ejemplo 20

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (505 mg) en acetato de etilo (10 ml) se añadieron piridina (0.5 ml) y cloruro de ciclohexansulfonilo (362 mg), y la mezcla se agitó a temperatura ambiente durante 3.5 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar una N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}ciclohexanosulfonamida (53 mg, rendimiento: 8%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.11 - 1.94 (10 H, m), 1.99 - 2.18 (2 H, m), 2.53 (2 H, t, J = 7.3 Hz), 2.66 - 2.94 (2 H,

m), 3.08 (2 H, m), 3.44 (3 H, s), 3.68 - 3.80 (2 H, m), 3.96 - 4.15 (2 H, m), 6.67 (1 H, d, J = 2.6 Hz), 6.84 (1 H, dd, J = 8.5, 2.4 Hz), 7.20 (1 H, d, J = 8.5 Hz), 8.00 (1 H, d, J = 2.1 Hz), 8.27 (1 H, d, J = 0.8 Hz).

Ejemplo 21

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (196 mg) en acetato de etilo (10 ml) se añadieron piridina (0.5 ml) y cloruro de 3-fenilpropansulfonilo (182 mg), y la mezcla se agitó a temperatura ambiente durante 1.5 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. El sólido obtenido se disolvió en una suspensión de carbón activado en acetato de etilo, y la mezcla se agitó durante 3 h, se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}-3-fenilpropan-1-sulfonamida (75 mg, rendimiento: 26%) en forma de cristales blancos. Punto de

fusión 101.8-102.0°C.

Ejemplo 22

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (234 mg) en acetato de etilo (10 ml) se añadieron piridina (5.0 ml) y cloruro de 4-clorobencensulfonilo (185 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 35:65, v/v). Se suspendió el carbón activado en la fracción eluida, y la mezcla se agitó durante 1 hora, se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 4-cloro-N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}bencensulfonamida (145 mg, rendimiento: 43%) en forma de cristales en pluma blancos. Punto de fusión 111-113°C.

Ejemplo 23

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

metoxietoxi)fenil]propan-1-amina (275 mg) en acetato de etilo (10 ml) se añadieron piridina (5.0 ml) y cloruro de 2-clorobencensulfonilo (227 mg), y la mezcla se agitó a temperatura ambiente durante 6 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un aceite de color amarillo pálido. El aceite obtenido se disolvió en una suspensión de carbón activado en acetato de etilo, y la mezcla se agitó durante 1 hora. La mezcla de reacción se filtró y se concentró para dar 2-cloro-N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}bencensulfonamida (10 mg, rendimiento: 3%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.63 - 1.81 (10 H, m), 2.46 (2 H, t, J = 7.3 Hz), 2.89 (2 H, q, J = 6.7 Hz), 3.43 (3 H, s), 3.69 - 3.76 (2 H, m), 4.01 - 4.12 (2 H, m), 5.00 (1 H, t, J = 6.0 Hz), 6.64 (1 H, d, J = 2.4 Hz), 6.79 (1 H, dd, J = 8.6, 2.5 Hz), 7.11 (1 H, d, J = 8.5 Hz), 7.30 - 7.45 (1 H, m), 7.50 (2 H, d, J = 3.8 Hz), 7.98 (1 H, d, J = 1.9 Hz), 8.06 (1 H, d, J = 7.7 Hz), 8.24 (1 H, s).

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Ejemplo 24

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (150 mg) en acetato de etilo (10 ml) se añadieron piridina (5.0 ml) y cloruro de 3-clorobencensulfonilo (191 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-cloro-N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}bencensulfonamida (40 mg, rendimiento: 19%) en forma de cristales en pluma blancos. Punto de fusión 110-114°C.

Ejemplo 25

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-amina (147 mg) en acetato de etilo (10 ml) se añadieron piridina (5.0 ml) y cloruro de 2-propansulfonilo (122 mg), y la mezcla se agitó a temperatura

ambiente durante 6 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v). Se suspendió el carbón activado en la fracción eluida, y la mezcla se agitó durante 1 hora. La mezcla de reacción se filtró y se concentró para dar N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}propan-2-sulfonamida (11 mg, rendimiento: 6%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.8 Hz), 1.61 - 2.07 (2 H, m), 2.53 (2 H, t, J = 7.3 Hz), 2.88 - 2.99 (1 H, m), 3.01 - 3.22 (2 H, m), 3.38 - 3.48 (3 H, m), 3.64 - 3.76 (2 H, m), 3.95 - 4.17 (2 H, m), 6.67 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.20 (1 H, d, J = 8.5 Hz), 8.00 (1 H, s), 8.27 (1 H, d, J = 1.1 Hz).

Ejemplo 26

Una solución de ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrílico (150 mg) y N,N'-carbonildiimidazol (67 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente

durante 1 hora. A esta mezcla se añadieron 3-metilbutano-1-sulfonamida (62 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.062 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:20 - 2:3, v/v) y se concentró. Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]acrilamida (124 mg, rendimiento: 62%) en forma de cristales incoloros. Punto de fusión 155.5-157.5°C.

Ejemplo 27

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-ol (2.26 g) en acetato de etilo (40 ml) se añadieron trietilamina (3.0 ml) y cloruro de metansulfonilo (1.2 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada

de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite anaranjado. A una solución del aceite obtenido en N,N-dimetilformamida (30 ml) se añadió ftalimida de potasio (1.02 g), y la mezcla se agitó a 80°C durante 2 h. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El sólido obtenido se lavó con éter diisopropílico y hexano para dar un sólido de color marrón. A una solución del sólido obtenido en metanol (100 ml) se añadió monohidrato de hidracina (2.19 g), y la mezcla se agitó a 50°C durante 1 hora. La mezcla de reacción se concentró, el residuo se lavó con éter dietílico, y el filtrado se concentró. El residuo obtenido se disolvió en acetato de etilo, y la capa orgánica se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-amina (1.30 g, rendimiento: 63%) en forma de un aceite marrón.

A una solución del aceite obtenido (480 mg) en acetato de etilo (10 ml) se añadieron piridina (0.50 ml) y cloruro de 1-pentansulfonilo (240 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. Se añadió ácido

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clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio N-{(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-il}pentan-1-sulfonamida (46 mg, rendimiento: 7%) en forma de cristales blancos. Punto de fusión 106.0-106.5°C.

Ejemplo 28

A una solución de trifosgeno (68 mg) en diclorometano (5 ml) se añadieron 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (205 mg) y piridina (0.10 ml) bajo enfriamiento con hielo, y la mezcla de reacción se concentró inmediatamente. A una solución del residuo obtenido en tetrahidrofurano (10 ml) se añadieron pentan-1-sulfonamida (125 mg), N,N-diisopropiletilamina (0.40 ml) y 4-dimetilaminopiridina (62 mg), y la mezcla se agitó a temperatura ambiente durante 10 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una

solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil(pentilsulfonil)carbamato de ter-butilo (35 mg, rendimiento: 12%) en forma de un polvo blanco. Punto de fusión 97.5-99.0°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.91 (3 H, t, J = 7.2 Hz), 1.21 - 1.52 (4 H, m), 1.71 - 1.90 (2 H, m), 1.89 - 2.05 (2 H, m), 2.58 (2 H, t, J = 7.3 Hz), 3.29 - 3.42 (2 H, m), 3.43 (3 H, s), 3.69 - 3.75 (2 H, m), 4.04 - 4.12 (2 H, m), 4.16 (2 H, t, J = 6.3 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.7, 2.4 Hz), 7.19 (1 H, d, J = 8.5 Hz), 7.34 (1 H, s), 8.02 (1 H, d, J = 2.1 Hz), 8.28 (1 H, d, J = 1.1 Hz).

Ejemplo 29

Se disolvió {3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}[(2-nitrofenil)sulfonil]carbamato de ter-butilo (3.44 g) en una solución en acetato de etilo 4 N de ácido clorhídrico (40 ml), y la mezcla se agitó a temperatura ambiente durante 3 horas y a 40°C durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico

concentrado (2.0 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó ácido trifluoroacético (4.0 ml), y la mezcla se siguió agitando durante 2 h. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:7, v/v) para dar una N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}-2-nitrobencensulfonamida (2.77 g, rendimiento: 95%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 125.5-126.0°C.

Ejemplo 30

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (400 mg) en acetonitrilo (10 ml) se añadieron N,N-diisopropiletilamina (0.40 ml) y p-toluensulfonilisocianato (202 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato

ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un aceite incoloro. El aceite obtenido se disolvió en acetato de etilo, se añadieron anhídrido acético (0.5 ml) y piridina (0.5 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar un aceite incoloro. El aceite obtenido se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio [(4-metilfenil)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo monohidratado (105 mg, rendimiento: 18%) en forma de cristales blancos. Punto de fusión 118-120°C.

Ejemplo 31

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

metoxietoxi)fenil]propan-1-ol (402 mg) en acetonitrilo (5 ml) se añadieron N,N-diisopropiletilamina (0.40 ml) y bencensulfonilisocianato (190 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadieron anhídrido acético (0.5 ml) y piridina (0.5 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un (fenilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (264.8 mg, rendimiento: 45%) en forma de un aceite incoloro. El aceite se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio cristales blancos en forma de 1.5 hidrato. Punto de fusión 174-177°C.

Ejemplo 32

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (397 mg) en acetonitrilo (5 ml)

se añadieron N,N-diisopropiletilamina (0.40 ml) y 4-clorobencensulfonilisocianato (218 mg), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadieron anhídrido acético (0.5 ml) y piridina (0.5 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido incoloro. La recristalización en acetato de etilo-hexano dio (4-clorofenil)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (161 mg, rendimiento: 26%) en forma de cristales blancos. Punto de fusión 147-150°C.

Ejemplo 33

A una solución de trifosgeno (130 mg) en tolueno (10 ml) se añadieron 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (399.8 mg) y piridina (0.10 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 5 min. Se añadieron 2-clorobencensulfonamida (208 mg), N,N-diisopropiletilamina (0.40 ml), 4-dimetilaminopiridina (148 mg) y tetrahidrofurano (30 ml) a la

mezcla de reacción, y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v), y luego se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar (2-clorofenil)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (216 mg, rendimiento: 35%) como una forma amorfa incolora.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.61 - 1.75 (2 H, m), 2.30 (2 H, t, J = 7.0 Hz), 3.41 (3 H, s), 3.62 - 3.73 (2 H, m), 3.76 - 3.86 (2 H, m), 3.97 - 4.07 (2 H, m), 6.60 (1 H, d, J = 2.4 Hz), 6.68 (1 H, dd, J = 8.4, 2.4 Hz), 7.00 (1 H, d, J = 8.5 Hz), 7.17 (1 H, s), 7.30 (2 H, s), 7.92 (1 H, d, J = 2.1 Hz), 8.07 (1 H, d, J = 7.9 Hz), 8.21 (1 H, d, J = 1.1 Hz).

Ejemplo 34

A una solución de trifosgeno (136 mg) en tolueno (10 ml) se añadieron 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (396.8 mg) y piridina (0.10 ml) bajo enfriamiento con hielo, y la mezcla se

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agitó durante 5 min. Se añadieron o-toluensulfonamida (181 mg), N,N-diisopropiletilamina (0.40 ml), 4-dimetilaminopiridina (142 mg) y tetrahidrofurano (30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v), se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un [(2-metilfenil)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (200 mg, rendimiento: 34%) como una forma amorfa incolora.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.59 - 1.83 (2 H, m), 2.27 - 2.41 (2 H, m), 2.56 (3 H, s), 3.41 (3 H, s), 3.60 - 3.76 (2 H, m), 3.76 - 3.91 (2 H, m), 3.98 - 4.05 (2 H, m), 6.61 (1 H, d, J = 2.4 Hz), 6.67 (1 H, d, J = 9.0 Hz), 6.96 - 7.22 (3 H, m), 7.32 (1 H, d, J = 5.5 Hz), 7.92 (1 H, d, J = 1.3 Hz), 7.97 (1 H, d, J = 7.3 Hz), 8.20 (1 H, s).

Ejemplo 35

A una solución de trifosgeno (122 mg) en tolueno (10

ml) se añadieron 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (386 mg) y piridina (0.10 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 5 min. Se añadieron butan-1-sulfonamida (142 mg), N,N-diisopropiletilamina (0.40 ml), 4-dimetilaminopiridina (122 mg) y tetrahidrofurano (30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v), se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar (butilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo monohidratado (54 mg, rendimiento: 10%) en forma de cristales blancos. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 94.0-96.0°C.

Ejemplo 36

A una solución de trifosgeno (142 mg) en tolueno (10 ml) se añadieron (2E)-3-[2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-ol (388 mg) y piridina (90 µl) bajo enfriamiento con hielo, y la mezcla se agitó durante 5 min. Se añadieron pentan-1-sulfonamida (194.5 mg), N,N-diisopropiletilamina (0.40 ml), 4-dimetilaminopiridina (125 mg) y tetrahidrofurano (30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 acetato de etilo solo, v/v), se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un (pentilsulfonil)carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-ilo (14 mg, rendimiento: 3%) como una forma amorfa blanca.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.90 (3 H, t, J = 7.1 Hz), 1.24 - 1.50 (4 H, m), 1.67 - 1.95 (2 H, m), 3.33 - 3.42 (2 H, m), 3.44 (3 H, s), 3.71 - 3.79 (2 H, m), 4.05 - 4.16 (2 H, m), 4.74 (2 H, dd, J = 6.7, 1.0 Hz), 5.97 - 6.31 (1 H, m), 6.55 - 6.73 (2 H, m), 6.88 (1 H, dd, J = 8.7, 2.4 Hz), 7.52 (1 H, d,

J = 8.7 Hz), 8.01 (1 H, d, J = 1.9 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 37

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-ol (184 mg) en acetonitrilo (2.5 ml) se añadieron N,N-diisopropiletilamina (0.40 ml) y 4-clorobencensulfonilisocianato (140 µl), y la mezcla se agitó a temperatura ambiente durante 30 min. Luego se añadió 4-clorobencensulfonilisocianato (90 µl), y la mezcla se agitó durante 10 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El aceite obtenido se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio [(4-clorofenil)sulfonil]carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-propen-1-ilo dihidratado (147 mg, rendimiento: 52%) en forma de cristales blancos. Punto de fusión 174.5°C (desc.).

Ejemplo 38

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

metoxietoxi)fenil]propiónico (1.90 g) en tolueno (25 ml) se añadieron trietilamina (0.90 ml) y difenilfosforilazida (1.40 ml), y la mezcla se agitó a 80°C durante 1 hora. Se añadió alcohol bencílico (0.80 ml), y la mezcla se agitó con calentamiento a reflujo durante 10 h. Tras enfriar hasta temperatura ambiente, la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar un {2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]etil}carbamato de bencilo (2.02 g, rendimiento: 89%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Punto de fusión 102.5-103.0°C.

A una solución de {2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]etil}carbamato de bencilo (450 mg) en tetrahidrofurano (5 ml) se añadió paladio sobre carbón al 10% (92 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. La mezcla de reacción se filtró y el filtrado se concentró para dar un aceite marrón.

El aceite obtenido se disolvió en acetato de etilo

(5 ml), se añadieron piridina (1 ml) y cloruro de 1-pentansulfonilo (227 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v) para dar N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]etil}pentan-1-sulfonamida (64 mg, rendimiento: 14%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.73 - 0.94 (3 H, m), 1.15 - 1.38 (4 H, m), 1.46 - 1.77 (2 H, m), 2.59 - 2.97 (4 H, m), 3.18 - 3.33 (2 H, m), 3.43 (3 H, s), 3.60 - 3.78 (2 H, m), 3.97 - 4.14 (2 H, m), 4.55 (1 H, t, J = 5.8 Hz), 6.43 - 6.71 (1 H, m), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.08 (1 H, d, J = 8.7 Hz), 7.94 (1 H, dd, J = 8.7, 2.3 Hz), 8.43 (1 H, s).

Ejemplo 39

A una solución de 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propan-1-amina (0.33 g) en acetonitrilo (8 ml) se añadió bencensulfonilisocianato (0.14 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Los cristales precipitados se recogieron por filtración, se lavaron con acetonitrilo y se secaron ($MgSO_4$)

para dar N-[({3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propil}amino)carbonil]bencensulfonamida (0.29 g, rendimiento: 57%) en forma de cristales incoloros. Punto de fusión 149°C.

Ejemplo 40

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butan-1-ol (1.00 g) en acetato de etilo (20 ml) se añadieron trietilamina (1.20 ml) y cloruro de metansulfonilo (0.70 ml), y la mezcla se agitó a temperatura ambiente. Al cabo de 1 hora, se añadieron trietilamina (1.20 ml) y cloruro de metansulfonilo (0.50 ml), y la mezcla se siguió agitando a temperatura ambiente durante 30 min. La mezcla de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite anaranjado.

A una solución de pentan-1-sulfonamida (679 mg) en N,N-dimetilformamida (10 ml) se añadió hidruro de sodio (60% en aceite, 198 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. A la mezcla de reacción se añadió gota a gota una solución del aceite anaranjado obtenido con anterioridad en N,N-dimetilformamida (20 ml), y la mezcla se agitó a 45°C durante 60 h. Tras enfriar hasta temperatura

ambiente, se añadió una solución acuosa saturada de cloruro de amonio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v) para dar N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butil}pentan-1-sulfonamida (238 mg, rendimiento: 18%) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.89 (3 H, t, J = 7.1 Hz), 1.19 (3 H, d, J = 7.0 Hz), 1.26 - 1.44 (4 H, m), 1.63 - 2.00 (4 H, m), 2.81 - 3.23 (5 H, m), 3.43 (3 H, s), 3.69 - 3.77 (2 H, m), 4.04 - 4.13 (2 H, m), 4.35 - 4.45 (1 H, m), 6.61 (1 H, d, J = 2.6 Hz), 6.90 (1 H, dd, J = 8.7, 2.6 Hz), 7.23 (1 H, d, J = 8.7 Hz), 8.01 (1 H, d, J = 2.3 Hz), 8.29 (1 H, d, J = 0.9 Hz).

Ejemplo 41

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilpropan-1-ol (1.22 g) en acetato de etilo (50 ml) se añadieron trietilamina (0.80 ml) y cloruro de metansulfonilo (0.35 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato

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ácido de sodio, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite amarillo.

A una solución de pentan-1-sulfonamida (890 mg) en N,N-dimetilformamida (10 ml) se añadió hidruro de sodio (60% en aceite, 233 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. A la mezcla de reacción se añadió gota a gota una solución del aceite anaranjado obtenido con anterioridad en N,N-dimetilformamida (10 ml), y la mezcla se agitó a 50°C durante 60 h. Tras enfriar hasta temperatura ambiente, se añadió una solución acuosa saturada de cloruro de amonio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 35:65, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio N-{3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilpropil}pentan-1-sulfonamida (355 mg, rendimiento: 22%) en forma de cristales blancos. Punto de fusión 80-82°C.

Ejemplo 42

A una solución de ácido 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}propiónico (1.01 g) en tetrahidrofurano (30 ml) se añadió N,N'-carbonildiimidazol (651 mg), y la mezcla se calentó a reflujo durante 1 h. Tras

enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (439 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.60 ml) se añadieron a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con solución acuosa saturada de cloruro de amonio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-{2-[(2,4-diclorobencil)oxi]-4-isopropoxifenil}-N-(pentilsulfonil)propanamida (713 mg, rendimiento: 52%) en forma de cristales blancos. Punto de fusión 120.0-120.5°C.

Ejemplo 43

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (4776 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (308 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metilbutano-1-sulfonamida (259 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.25 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N,

una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), luego se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(3-metilbutil)sulfonil]propanamida (137 mg, rendimiento: 22%) en forma de cristales blancos. Punto de fusión 130-132°C.

Ejemplo 44

A una solución de 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}propionato de etilo (3.31 g) en tetrahidrofurano (15 ml) y etanol (15 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (15.0 ml), y la mezcla se agitó a 50°C durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (15.0 ml), y la mezcla se diluyó con tolueno y se concentró. El residuo se disolvió en acetato de etilo. La capa orgánica se lavó dos veces con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar ácido 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-

oxoetoxi]fenil}propiónico (2.91 g, rendimiento: 93%) en forma de un sólido de color amarillo pálido.

A una solución de ácido 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}propiónico (2.23 g) en tetrahidrofurano (30 ml) se añadió N,N'-carbonildiimidazol (1.17 g), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (1.07 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (1.00 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 7:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio una 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}-N-(pentilsulfonil)propanamida (1.96 g, rendimiento: 69%) en forma de un polvo blanco. Punto de fusión 111-113°C.

Ejemplo 45

A una solución de un producto crudo purificado (0.67 g) de ácido 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-

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il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}propiónico en tetrahidrofurano (30 ml) se añadió N,N'-carbonildiimidazol (363 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metilbutano-1-sulfonamida (343 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.50 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 7:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio una 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}-N-[(3-metilbutil)sulfonil]propanamida (285 mg, rendimiento: 33%) en forma de cristales en pluma blancos. Punto de fusión 123-125°C.

Ejemplo 46

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (945 mg) en tetrahidrofurano (40 ml) se añadió N,N'-carbonildiimidazol (622 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura

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ambiente, se añadieron 3-metoxipropano-1-sulfonamida (415 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.60 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v), luego se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(3-metoxipropil)sulfonil]propanamida (622 mg, rendimiento: 50%) en forma de cristales en pluma blancos. Punto de fusión 112-113°C.

Ejemplo 47

A una solución de ácido 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}propanoico (0.70 g) en tetrahidrofurano (15 ml) se añadió N,N'-carbonildiimidazol (392 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (342 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.50 ml) a la mezcla de

reacción, y la mezcla se agitó durante la noche. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 acetato de etilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio una 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-oxopirrolidin-1-il)etoxi]fenil}-N-(pentilsulfonil)propanamida (668 mg, rendimiento: 74%) en forma de un polvo blanco. Punto de fusión 123-126°C.

Ejemplo 48

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (0.30 g) en N,N-dimetilformamida (7 ml) se añadió N,N'-carbonildiimidazol (0.18 g), y la mezcla se agitó a 60°C durante 1.5 h. Se añadió morfolina (193 µl) a la mezcla de reacción, y la mezcla se agitó durante la noche. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se

sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (5:95 - 3:7, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio morfolin-4-carboxilato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (372 mg, rendimiento: 98%) en forma de un polvo blanco. Punto de fusión 82.3-82.4°C.

Ejemplo 49

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (0.30 g) en N,N-dimetilformamida (7 ml) se añadió N,N'-carbonildiimidazol (0.18 g), y la mezcla se agitó a 60°C durante 1 hora. Se añadió 1-butilamina (0.22 ml) a la mezcla de reacción, y la mezcla se agitó durante 6 h. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:7, v/v) para dar un sólido blanco. La recristalización en éter diisopropílico-hexano dio butilcarbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (297 mg, rendimiento: 80%) en forma de un polvo blanco. Punto de fusión 91.7-91.8°C.

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Ejemplo 50

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (0.30 g) en N,N-dimetilformamida (7 ml) se añadió N,N'-carbonildiimidazol (0.18 g), y la mezcla se agitó a 60°C durante 1 hora. Se añadió N-metil-1-butilamina (0.26 ml) a la mezcla de reacción, y la mezcla se agitó durante 6.5 h. También se agregó N-metil-1-butilamina (0.26 ml), y la mezcla se agitó durante la noche. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:7, v/v) para dar un sólido blanco. La recristalización en hexano dio butil(metil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (271 mg, rendimiento: 73%) en forma de un polvo blanco. Punto de fusión 54.0-55.2°C.

Ejemplo 51

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (0.30 g) en N,N-dimetilformamida (7 ml) se añadió N,N'-carbonildiimidazol (0.18 g), y la mezcla se agitó a 60°C durante 1.5 h. Se agregó ciclopropilmetilamina

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(385 µl) a la mezcla de reacción, y la mezcla se agitó durante la noche. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:7, v/v) para dar un sólido blanco. La recristalización en éter diisopropílico-hexano dio (ciclopropilmetil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (272 mg, rendimiento: 73%) en forma de un polvo blanco. Punto de fusión 87.8-87.9°C.

Ejemplo 52

A una solución de (ciclopropilmetil)carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propilo (342 mg) en N,N-dimetilformamida (5 ml) se añadieron carbonato de potasio (225 mg) y 2-cloro-N,N-dietilacetamida (182 mg), y la mezcla se agitó a 50°C durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 -

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3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (ciclopropilmetil)carbamato de 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(dietilamino)-2-oxoetoxi]fenil}propilo (346 g, rendimiento: 81%) en forma de cristales blancos. Punto de fusión 94.0-94.5°C.

Ejemplo 53

A una solución de (ciclopropilmetil)carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-hidroxifenil)propilo (381 mg) en N,N-dimetilformamida (5 ml) se añadieron carbonato de potasio (252 mg) y bromoacetato de etilo (0.20 ml), y la mezcla se agitó a 50°C durante 30 min. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar {3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-({[(ciclopropilmetil)amino]carbonil}-oxi)propil]fenoxi}acetato de etilo (383 mg, rendimiento: 84%) en forma de un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales en pluma blancos. Punto de fusión 112.8-113.0°C.

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Ejemplo 54

A una solución de {3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-({[(ciclopropilmetil)amino]carbonil}oxi)propil]fenoxi}acetato de etilo (301 mg) en tetrahidrofurano (5 ml) y etanol (5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (2.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N (2.0 ml) a la mezcla de reacción, se diluyó con tolueno y se concentró. El residuo se disolvió en acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se recristalizó en acetato de etilo-hexano para dar ácido {3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-({[(ciclopropilmetil)amino]carbonil}oxi)propil]fenoxi}acético (284 mg, rendimiento: cuant.) en forma de cristales en pluma blancos.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.14 - 0.21 (2 H, m), 0.42 - 0.53 (2 H, m), 0.85 - 1.05 (1 H, m), 1.74 - 1.97 (2 H, m), 2.48 - 2.58 (2 H, m), 2.96 - 3.06 (2 H, m), 4.02 (2 H, t, J = 6.3 Hz), 4.64 (2 H, s), 4.72 (1 H, s), 6.71 (1 H, d, J = 2.6 Hz), 6.82 (1 H, dd, J = 8.5, 2.4 Hz), 7.24 (1 H, d, J = 8.7 Hz), 7.99 (1 H, d, J = 2.1 Hz), 8.26 (1 H, d, J = 0.9 Hz).

Ejemplo 55

A una solución de 3-[2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (400 mg) en N,N-dimetilformamida (5 ml) se añadió N,N'-carbonildiimidazol (222 mg), y la mezcla se agitó a 40°C durante 1 hora. Se añadió 3-metoxipropilamina (0.55 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (3-metoxipropil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (276 mg, rendimiento: 54%) en forma de cristales en pluma blancos. Punto de fusión 83.5-85.0°C.

Ejemplo 56

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (405 mg) en N,N-dimetilformamida (5 ml) se añadió N,N'-carbonildiimidazol (224 mg), y la mezcla se agitó a 40°C durante 1 hora. Se añadió 2-etoxietilamina (0.55 ml) a la mezcla de reacción, y la mezcla se agitó

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durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2-etoxietil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (250 mg, rendimiento: 48%) en forma de un polvo blanco. Punto de fusión 66-68°C.

Ejemplo 57

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]acrílico (598.8 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (368 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metoxipropano-1-sulfonamida (355 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.40 ml) a la mezcla de reacción, y la mezcla se agitó durante 3 h. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró.

El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5 - 9:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil]-N-[(3-metoxipropil)sulfonil]acrilamida (296 mg, rendimiento: 37%) en forma de un polvo blanco. Punto de fusión 129.5-130.0°C.

Ejemplo 58

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoxietoxi)fenil]metanol (473 mg) en N,N-dimetilformamida (5 ml) se añadió N,N'-carbonildiimidazol (295.3 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora y a 40°C durante 30 min. Luego se añadieron pentan-1-sulfonamida (289 mg), 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) y 4-dimetilaminopiridina (215 mg), y la mezcla se agitó posteriormente durante la noche. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:7 - 1:4, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (pentilsulfonil)carbamato de 2-

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{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (373 mg, rendimiento: 54%) en forma de cristales blancos. Punto de fusión 130-132°C.

Ejemplo 59

A una solución de trifosgeno (445 mg) en tolueno (10 ml) se añadió una solución de 3-metilbutano-1-sulfonamida (659 mg) en tolueno (5 ml) y piridina (0.40 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1 hora. Luego se agregaron [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (1.12 g), N,N-diisopropiletilamina (0.75 ml), 4-dimetilaminopiridina (574 mg) y tetrahidrofurano (15 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio [(3-metilbutil)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (19 mg, rendimiento: 2%) en forma de cristales en pluma blancos. Punto de fusión 122-124°C.

Ejemplo 60

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (501 mg) en tolueno (20 ml) y tetrahidrofurano (5 ml) se añadió clorosulfonilisocianato (120 µl) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se añadió piridina (0.25 ml). Al cabo de 1 hora, se añadió isobutilamina (0.75 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:2, v/v), y se recristalizó en acetato de etilo-hexano para dar [(isobutilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (13 mg, rendimiento: 2%) en forma de cristales blancos. Punto de fusión 160-161°C.

Ejemplo 61

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (507 mg) en tolueno (20 ml) y tetrahidrofurano (5 ml) se añadió clorosulfonilisocianato (120

µl) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se añadió piridina (0.25 ml). Al cabo de 1 hora, se agregó 1-pentilamina (0.75 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:2, v/v), y se recristalizó en acetato de etilo-hexano para dar [(pentilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (33 mg, rendimiento: 4%) en forma de cristales blancos. Punto de fusión 153-155°C.

Ejemplo 62

A una solución de (4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)metanol (1.04 g) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (592 mg), y la mezcla se agitó a 40°C durante 1 hora. Luego se agregaron pentan-1-sulfonamida (584 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.60 ml), y la mezcla se agitó posteriormente durante 2 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa

orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (pentilsulfonil)carbamato de 4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}bencilo (379 mg, rendimiento: 25%) en forma de un polvo blanco. Punto de fusión 124.5-125.5°C.

Ejemplo 63

A una solución de (2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)metanol (1.00 g) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (621 mg), y la mezcla se agitó a 40°C durante 1 hora. Luego se agregaron pentan-1-sulfonamida (594 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.60 ml), y la mezcla se agitó posteriormente durante 2 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55, v/v) para dar

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un sólido blanco. La recristalización en acetato de etilo-hexano dio (pentilsulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxibencilo (500 mg, rendimiento: 34%) en forma de un polvo blanco. Punto de fusión 70-73°C.

Ejemplo 64

A una solución de propan-1-sulfonato de 3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(hidroximetil)fenilo (1.02 g) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (613 mg), y la mezcla se agitó a 40°C durante 1 hora. Luego se agregaron pentan-1-sulfonamida (569 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.60 ml), y la mezcla se agitó posteriormente durante 2 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio propan-1-sulfonato de 3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[({[(pentilsulfonil)amino]carbonil}oxi)metil]fenilo (127 mg, rendimiento: 13%) en forma de cristales en pluma blancos.

Punto de fusión 86-89°C.

Ejemplo 65

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (1.08 g) en tetrahidrofurano (15 ml) se añadieron N,N-diisopropiletilamina (0.50 ml), 4-clorobencensulfonilisocianato (0.44 ml) y 4-dimetilaminopiridina (355 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. También se agregó 4-clorobencensulfonilisocianato (0.44 ml), y la mezcla se agitó durante 1 hora. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido incoloro. La recristalización en acetato de etilo-hexano dio [(4-clorofenil)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (264 mg, rendimiento: 16%) en forma de un polvo blanco. Punto de fusión 112-115°C.

Ejemplo 66

A una solución de [2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (520 mg) en tolueno (20 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se añadió piridina (0.30 ml). Al cabo de 1 hora, se añadió 1-butilamina (0.80 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio [(butilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (542 mg, rendimiento: 71%) en forma de un polvo blanco. Punto de fusión 164-165°C.

Ejemplo 67

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (521 mg) en tolueno (20 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se añadió piridina (0.30 ml), y al cabo de 1 h, se agregó ciclopropilmetilamina (750 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de

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reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. El sólido obtenido se lavó con éter diisopropílico, y se recristalizó en acetato de etilo-éter diisopropílico para dar {[(ciclopropilmetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (481 mg, rendimiento: 63%) en forma de un polvo blanco. Punto de fusión 150.0-150.5°C.

Ejemplo 68

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (513 mg) en tolueno (20 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se agregó piridina (0.30 ml). Al cabo de 1 hora, se añadió p-cloroanilina (659 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. El sólido obtenido se lavó con éter diisopropílico, y se recristalizó en acetato de

etilo-éter diisopropílico para dar {[(4-clorofenil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (32.1 mg, rendimiento: 4%) en forma de un polvo blanco. Punto de fusión 159°C (desc.).

Ejemplo 69

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (541 mg) en tolueno (20 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se agregó piridina (0.30 ml). Al cabo de 1 hora, se agregó morfolina (0.80 ml), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar (morfolin-4-ilsulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (65 mg, 8%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.24 - 3.34 (4 H, m), 3.44 (3 H, s), 3.59 - 3.79 (6 H, m), 4.07 - 4.18 (2 H, m), 5.10 (2

H, s), 6.71 (1 H, s), 6.75 (1 H, d, J = 2.4 Hz), 6.88 (1 H, dd, J = 8.6, 2.5 Hz), 7.41 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 1.9 Hz), 8.27 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo 70

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (506 mg) en tolueno (20 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se agregó piridina (0.30 ml). Al cabo de 1 hora, se agregó 1-hexilamina (0.80 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) y se recristalizó en acetato de etilo-éter diisopropílico para dar [(hexilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (71 mg, rendimiento: 9%) en forma de cristales blancos.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.79 - 0.97 (3 H, m), 1.17 - 1.38 (6 H, m), 1.40 - 1.55 (2 H, m), 2.94 (2 H, q, J = 7.0 Hz), 3.44 (3 H, s), 3.69 - 3.79 (2 H, m), 4.07 - 4.15 (2 H,

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m), 5.14 (2 H, s), 5.19 (1 H, t, J = 6.2 Hz), 6.73 (1 H, d, J = 2.4 Hz), 6.87 (1 H, dd, J = 8.5, 2.4 Hz), 7.15 (1 H, s), 7.42 (1 H, d, J = 8.5 Hz), 8.02 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 71

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (500 mg) en N,N-dimetilformamida (5 ml) se añadió N,N'-carbonildiimidazol (337 mg), y la mezcla se agitó a 40°C durante 1 hora. Luego se agregaron N-hexil-N-metilsulfamida (389 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml), y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar {[hexil(metil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (85 mg, rendimiento: 11%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.76 - 0.97 (3 H, m), 1.14 - 1.36 (4 H, m), 1.41 - 1.64 (4 H, m), 2.87 (3 H, s), 3.09 - 3.23 (2 H, m), 3.44 (3 H, s), 3.67 - 3.85 (2 H, m), 4.07 -

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4.18 (2 H, m), 5.08 (2 H, s), 6.74 (1 H, d, J = 2.4 Hz), 6.87 (1 H, dd, J = 8.6, 2.5 Hz), 7.04 (1 H, s), 7.41 (1 H, d, J = 8.5 Hz), 8.00 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 72

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (511 mg) en tetrahidrofurano (6 ml) se añadió N,N'-carbonildiimidazol (314 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron N-hexil-N-metilsulfamida (250 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 10 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-{[hexil(metil)amino]sulfonil}propanamida (59 mg, rendimiento: 8%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.83 - 0.93 (3 H, m), 1.19 - 1.37 (6 H, m), 1.44 - 1.57 (2 H, m), 2.52 (2 H, t, J = 7.3

Hz), 2.76 (3 H, s), 2.89 (2 H, t, J = 7.3 Hz), 3.01 - 3.12 (2 H, m), 3.42 (3 H, s), 3.68 - 3.74 (2 H, m), 3.97 - 4.11 (2 H, m), 6.56 (1 H, d, J = 2.4 Hz), 6.79 (1 H, dd, J = 8.5, 2.6 Hz), 7.19 (1 H, d, J = 8.7 Hz), 8.05 (1 H, d, J = 1.9 Hz), 8.35 (1 H, dd, J = 2.1, 0.8 Hz), 8.67 (1 H, s).

Ejemplo 73

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propiónico (508 mg) en tetrahidrofurano (5 ml) se añadió N,N'-carbonildiimidazol (296.1 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron sulfamida (221 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se recristalizó en tetrahidrofurano-éter diisopropílico para dar N-(aminosulfonil)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanamida (489 mg, rendimiento: 81%) en forma de un polvo blanco. Punto de fusión 158-159°C.

Ejemplo 74

A una solución de ácido 4-[2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoico (550.1 mg) en tetrahidrofurano (5 ml) se añadió N,N'-carbonildiimidazol (321 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (261 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 4-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)butanamida (151 mg, rendimiento: 21%) en forma de cristales en pluma blancos. Punto de fusión 96-97°C.

Ejemplo 75

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (500 mg) en diclorometano (15 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se agregó piridina (0.30 ml). Al cabo de 1 hora, se agregó 3-metoxipropilamina

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(0.80 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi){[(3-metoxipropil)amino]sulfonil}carbamato de bencilo (458 mg, rendimiento: 61%) en forma de cristales en pluma blancos. Punto de fusión 149.0-149.5°C.

Ejemplo 76

A una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (455 mg) en diclorometano (15 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo agitación con enfriamiento con hielo, y 30 min más tarde, se agregó piridina (0.30 ml). Al cabo de 1 hora, se agregó 2-etoxietilamina (0.80 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró

y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(2-etoxietil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (301 mg, rendimiento: 44%) en forma de cristales en pluma blancos. Punto de fusión 142.5-143.0°C.

Ejemplo 77

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoico (518.8 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (309 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (218 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)butanamida (251 mg, rendimiento: 37%) en forma de cristales blancos. Punto de fusión 136.9-137.1°C.

Ejemplo 78

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]butanoico (511 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (290 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metoxipropano-1-sulfonamida (230 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 4:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(3-metoxipropil)sulfonil]butanamida (330 mg, rendimiento: 49%) en forma de cristales blancos. Punto de fusión 107-109°C.

Ejemplo 79

A una solución de 3-[2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (2.01 g) en tetrahidrofurano (100 ml) se añadió trifenilfosfina (1.81 g), [(2-nitrofenil)sulfonil]carbamato de ter-butilo (1.81 g), y solución toluénica al 40% de azodicarboxilato de dietilo (3.80 ml) bajo enfriamiento con hielo, y la mezcla se agitó a 0°C durante 10 min y a temperatura ambiente durante 1 h. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 7:3, v/v) para dar {3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propil}[(2-nitrofenil)sulfonil]carbamato de ter-butilo (3.44 g, rendimiento: cuant.) en forma de un sólido de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.26 - 1.32 (9 H, m), 1.96 - 2.08 (2 H, m), 2.46 - 2.59 (2 H, m), 3.44 (3 H, s), 3.67 - 3.77 (4 H, m), 4.03 - 4.14 (2 H, m), 6.69 (1 H, d, J = 2.6 Hz), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.22 - 7.25 (1 H, m), 7.67 - 7.77 (3 H, m), 7.98 (1 H, d, J = 2.3 Hz), 8.22 - 8.30 (2 H, m).

Ejemplo 80

Una mezcla de ácido 3-[1-(2,4-difluorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (140 mg), N,N'-carbonildiimidazol (77 mg) y tetrahidrofurano (5.0 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar

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hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (72 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (72 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-difluorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (50 mg, rendimiento: 25%) en forma de cristales incoloros. Punto de fusión 107-108°C.

Ejemplo 81

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (254 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2,

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v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (450 mg, rendimiento: 66%) en forma de cristales incoloros. Punto de fusión 126-129°C.

Ejemplo 82

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron bencensulfonamida (264 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(fenilsulfonil)propanamida (170 mg, rendimiento: 24%) en forma de cristales incoloros. Punto de fusión 184-185°C.

Ejemplo 83

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 4-

(trifluorometil)bencensulfonamida (378 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-{[4-(trifluorometil)fenil]sulfonil}propanamida (700 mg, rendimiento: 89%) en forma de cristales incoloros. Punto de fusión 167-169°C.

Ejemplo 84

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 1-fenilmetansulfonamida (320 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se cristalizó en acetato de etilo-hexano para dar N-(bencilsulfonil)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanamida (620 mg, rendimiento:

87%) en forma de cristales incoloros. Punto de fusión 183-184°C.

Ejemplo 85

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron propan-1-sulfonamida (240 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(propilsulfonil)propanamida (520 mg, rendimiento: 80%) en forma de cristales incoloros. Punto de fusión 124-126°C.

Ejemplo 86

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (370 mg), N,N'-carbonildiimidazol (253 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron butan-1-sulfonamida

(171 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (237 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(butilsulfonil)-propanamida (450 mg, rendimiento: 66%) en forma de cristales incoloros. Punto de fusión 133-134°C.

Ejemplo 87

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron hexano-1-sulfonamida (278 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano

para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(hexilsulfonil)propanamida (340 mg, rendimiento: 48%) en forma de cristales incoloros. Punto de fusión 103-106°C.

Ejemplo 88

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 2-metilbencensulfonamida (288 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-[(2-metilfenil)sulfonil]propanamida (260 mg, rendimiento: 36%) en forma de cristales incoloros. Punto de fusión 165-166°C.

Ejemplo 89

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se

agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron propan-2-sulfonamida (207 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(isopropilsulfonil)propanamida (350 mg, rendimiento: 54%) en forma de cristales incoloros. Punto de fusión 135-136°C.

Ejemplo 90

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron ciclohexansulfonamida (274 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (427 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El

residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar N-(ciclohexilsulfonil)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanamida (390 mg, rendimiento: 55%) en forma de cristales incoloros. Punto de fusión 137-138°C.

Ejemplo 91

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (341 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-fenilpropan-1-sulfonamida (334 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (427 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-[(3-fenilpropil)sulfonil]propanamida (570 mg, rendimiento: 76%) en forma de cristales incoloros. Punto de fusión 132-134°C.

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Ejemplo 92

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (400 mg), N,N'-carbonildiimidazol (272 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metilbutil-1-sulfonamida (203 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (256 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]propanamida (400 mg, rendimiento: 73%) en forma de cristales incoloros. Punto de fusión 143-145°C.

Ejemplo 93

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (356 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (267 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (336 mg). La

mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (470 mg, rendimiento: 67%) en forma de cristales incoloros. Punto de fusión 115-117°C.

Ejemplo 94

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]acrílico (500 mg), N,N'-carbonildiimidazol (343 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (256 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (322 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-

pirazol-5-il]-N-(pentilsulfonil)acrilamida (220 mg, rendimiento: 32%) en forma de cristales incoloros. Punto de fusión 109-112°C.

Ejemplo 95

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]acrílico (410 mg), N,N'-carbonildiimidazol (274 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (220 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (276 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-isopropil-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (140 mg, rendimiento: 24%) en forma de cristales incoloros. Punto de fusión 149-151°C.

Ejemplo 96

Una mezcla de ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}propanoico (500 mg), N,N'-carbonildiimidazol (323 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras

enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (241 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (305 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:16 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropil-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (260 mg, rendimiento: 38%) en forma de cristales incoloros. Punto de fusión 144-145°C.

Ejemplo 97

Una mezcla de ácido 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoico (500 mg), N,N'-carbonildiimidazol (328 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (245 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (309 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de

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sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (450 mg, rendimiento: 66%) en forma de cristales incoloros. Punto de fusión 104-105°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.85 - 1.00 (6 H, m), 1.24 - 1.87 (10 H, m), 2.53 - 2.63 (2 H, m), 2.75 - 2.86 (2 H, m), 3.33 - 3.43 (2 H, m), 4.08 (2 H, t, J = 6.6 Hz), 5.19 (2 H, s), 5.53 (1 H, s), 6.56 (1 H, d, J = 8.5 Hz), 7.15 (1 H, dd, J = 8.5, 2.2 Hz), 7.39 (1 H, d, J = 2.2 Hz), 8.17 (1 H, brs).

Ejemplo 98

Una mezcla de ácido (2E)-3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrílico (2.50 g), N,N'-carbonildiimidazol (1.65 g) y tetrahidrofurano (50 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (1.23 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (1.55 g), la mezcla se agitó a temperatura ambiente durante 15 h, luego se agitó con calentamiento a reflujo durante 2 h y se concentró. Se agregó ácido clorhídrico 1 N (100 ml) al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano

para dar (2E)-3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (1.01 g, rendimiento: 30%) en forma de cristales incoloros. Punto de fusión 95-98°C.

Ejemplo 99

A una solución de ácido (2E)-3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acrílico (820 mg) en tetrahidrofurano (15 ml) se añadieron cloruro de tionilo (528 mg) y N,N-dimetilformamida (20 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. La mezcla de reacción se concentró. A una solución del residuo en tetrahidrofurano (15 ml) se añadieron 3-metilbutan-1-sulfonamida (403 mg), N,N-diisopropiletilamina (861 mg) y 4-dimetilaminopiridina (271 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 horas y se concentró. Se añadió ácido clorhídrico 1 N (100 ml) al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]acrilamida (540 mg, rendimiento: 48%) en forma de cristales incoloros. Punto de fusión 119-120°C.

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Ejemplo 100

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]propanoico (2.00 g), N,N'-carbonildiimidazol (1.30 g) y tetrahidrofurano (35 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (967 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (1.22 g). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:100 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-fenil-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (290 mg, rendimiento: 11%) en forma de cristales incoloros. Punto de fusión 145-147°C.

Ejemplo 101

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]propanoico (750 mg), N,N'-carbonildiimidazol (489 mg) y tetrahidrofurano (20 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (365 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (459 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se

concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (310 mg, rendimiento: 30%) en forma de cristales incoloros. Punto de fusión 108-112°C.

Ejemplo 102

Una mezcla de ácido 3-[3-(benciloxi)-1-(2,4-diclorobencil)-1H-pirazol-5-il]propanoico (400 mg), N,N'-carbonildiimidazol (240 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (179 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (226 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:25 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[3-(benciloxi)-1-(2,4-diclorobencil)-1H-pirazol-5-

il]-N-(pentilsulfonil)propanamida (300 mg, rendimiento: 56%) en forma de cristales incoloros. Punto de fusión 139-141°C.

Ejemplo 103

Bajo enfriamiento con hielo, a una solución de ácido (2E)-3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (730 mg) en tetrahidrofurano (7.0 ml) se añadieron sucesivamente cloruro de tionilo (471 mg) y N,N-dimetilformamida (20 mg), y la mezcla se agitó durante 1 hora. La mezcla de reacción se concentró. El residuo se disolvió en tetrahidrofurano (10 ml) y pentan-1-sulfonamida (179 mg), se añadieron N,N-diisopropiletilamina (768 mg) y 4-dimetilaminopiridina (242 mg) bajo enfriamiento con hielo. La mezcla se dejó calentar hasta temperatura ambiente, se agitó durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:12 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)acrilamida (250 mg, rendimiento: 25%) en forma de cristales incoloros. Punto de fusión 159-160°C.

Ejemplo 104

Una mezcla de ácido 3-{3-butoxi-1-[4-

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(trifluorometil)bencil]-1H-pirazol-5-il}propanoico (680 mg), N,N'-carbonildiimidazol (448 mg) y tetrahidrofurano (12 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (334 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (421 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v) para dar 3-{3-butoxi-1-[4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (170 mg, rendimiento: 18%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.88 (3 H, t, J = 7.1 Hz), 0.94 (3 H, t, J = 7.4 Hz), 1.23 - 1.51 (6 H, m), 1.63 - 1.80 (4 H, m), 2.50 - 2.62 (2 H, m), 2.71 - 2.83 (2 H, m), 3.27 - 3.40 (2 H, m), 4.06 (2 H, t, J = 6.6 Hz), 5.21 (2 H, s), 5.51 (1 H, s), 7.17 (2 H, d, J = 8.3 Hz), 7.55 (2 H, d, J = 8.3 Hz).

Ejemplo 105

Una mezcla de ácido 3-{1-(2,4-diclorobencil)-3-[(5-metil-1.3,4-oxadiazol-2-il)metoxi]-1H-pirazol-5-il}propanoico (250 mg), N,N'-carbonildiimidazol (148 mg) y tetrahidrofurano (5.0 ml) se agitó con calentamiento a reflujo durante 1 h.

Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (97 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (139 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:12 - 2:1, v/v), acetato de etilo y metanol-cloroformo (1:16 - 1:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-{1-(2,4-diclorobencil)-3-[(5-metil-1.3,4-oxadiazol-2-il)metoxi]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (210 mg, rendimiento: 63%) en forma de cristales incoloros. Punto de fusión 156-158°C.

Ejemplo 106

A una solución de ácido (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (690 mg) en tetrahidrofurano (7.0 ml) se añadieron cloruro de tionilo (407 mg) y N,N-dimetilformamida (20 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. La mezcla de reacción se concentró. A una solución del residuo en tetrahidrofurano (10 ml) se añadieron pentan-1-sulfonamida (272 mg), N,N-diisopropiletilamina (663 mg) y 4-dimetilaminopiridina (209 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 horas y

se concentró. Se añadió ácido clorhídrico 1 N (100 ml) al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:12 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)acrilamida (370 mg, rendimiento: 40%) en forma de cristales incoloros. Punto de fusión 130-132°C.

Ejemplo 107

Una mezcla de ácido 3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoico (600 mg), N,N'-carbonildiimidazol (360 mg) y N,N-dimetilformamida (15 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron pentan-1-sulfonamida (269 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (338 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-{3-butoxi-1-

[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (320 mg, rendimiento: 40%) en forma de cristales incoloros. Punto de fusión 131-133°C.

Ejemplo 108

Una mezcla de ácido 3-[1-(2,4-diclorobencil)-3-(piridin-2-ilmetoxi)-1H-pirazol-5-il]propanoico (760 mg), N,N'-carbonildiimidazol (455 mg) y N,N-dimetilformamida (15 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (297 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (428 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadieron ácido clorhídrico 1 N (200 ml) y acetato de etilo (20 ml) al concentrado, y el precipitado resultante se recogió por filtración para dar clorhidrato de 3-[1-(2,4-diclorobencil)-3-(piridin-2-ilmetoxi)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (500 mg, rendimiento: 46%) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.81 (3 H, t, J = 7.2 Hz), 1.14 - 1.38 (4 H, m), 1.52 - 1.67 (2 H, m), 2.57 - 2.67 (2 H, m), 2.71 - 2.83 (2 H, m), 3.27 - 3.37 (2 H, m), 5.20 (2 H, s), 5.28 (2 H, s), 5.71 (1 H, s), 6.63 (1 H, d, J = 8.4 Hz), 7.35 (1 H, dd, J = 2.1, 8.4 Hz), 7.56 - 7.74 (3 H, m), 8.08 - 8.18 (1 H, m), 8.67 (1 H, d, J = 4.8 Hz), 11.71 (1 H, m).

Ejemplo 109

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-3-

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(2-metoxietoxi)-1H-pirazol-5-il]acrílico (520 mg), N,N'-carbonildiimidazol (341 mg) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron pentan-1-sulfonamida (254 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (25 mg, rendimiento: 4%) en forma de cristales incoloros. Punto de fusión 82-85°C.

Ejemplo 110

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]acrílico (520 mg), N,N'-carbonildiimidazol (341 mg) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron 3-metilbutano-1-sulfonamida (254 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (320 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido

clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-(2-metoxietoxi)-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]acrilamida (310 mg, rendimiento: 44%) en forma de cristales incoloros. Punto de fusión 110-114°C.

Ejemplo 111

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}acrílico (600 mg), N,N'-carbonildiimidazol (375 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron pentan-1-sulfonamida (279 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (352 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}-

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N-(pentilsulfonil)acrilamida (250 mg, rendimiento: 44%) en forma de cristales incoloros. Punto de fusión 139-140°C.

Ejemplo 112

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}acrílico (600 mg), N,N'-carbonildiimidazol (375 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron 3-metilbutan-1-sulfonamida (279 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (352 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}-N-[(3-metilbutil)sulfonil]acrilamida (250 mg, rendimiento: 44%) en forma de cristales incoloros. Punto de fusión 139-140°C.

Ejemplo 113

Una mezcla de ácido (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-[(3-metiloxetan-3-il)metoxi]-1H-pirazol-5-il}acrílico (460 mg), N,N'-carbonildiimidazol (226

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mg) y N,N-dimetilformamida (15 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron pentan-1-sulfonamida (169 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (213 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 4:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-[(3-metiloxetan-3-il)metoxi]-1H-pirazol-5-il}-N-(pentilsulfonil)acrilamida (200 mg, rendimiento: 38%) en forma de cristales incoloros. Punto de fusión 144-147°C.

Ejemplo 114

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]acrílico (1.00 g), N,N'-carbonildiimidazol (686 mg) y N,N-dimetilformamida (25 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron 3-metilbutan-1-sulfonamida (512 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (645 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato

de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)]-3-isopropoxi-1H-pirazol-5-il}-N-[(3-metilbutil)sulfonil]acrilamida (380 mg, rendimiento: 28%) en forma de cristales incoloros. Punto de fusión 132-135°C.

Ejemplo 115

Una mezcla de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}acrílico (640 mg), N,N'-carbonildiimidazol (401 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron 3-metoxipropano-1-sulfonamida (303 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (378 mg), y la mezcla se agitó a 100°C durante 4 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}-N-[(3-metoxipropil)sulfonil]acrilamida (510 mg,

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rendimiento: 59%) en forma de cristales incoloros. Punto de fusión 138-139°C.

Ejemplo 116

A una solución de ácido (2E)-3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrílico (660 mg) en tetrahidrofurano (10 ml) se añadieron cloruro de tionilo (395 mg) y N,N-dimetilformamida (20 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. La mezcla de reacción se concentró. A una solución del residuo en tetrahidrofurano (10 ml) se añadieron pentan-1-sulfonamida (301 mg), N,N-diisopropiletilamina (644 mg) y 4-dimetilaminopiridina (203 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 horas y se concentró. Se añadió ácido clorhídrico 1 N (100 ml) al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (160 mg, rendimiento: 18%) en forma de cristales de color amarillo pálido. Punto de fusión 154-157°C.

1029

Ejemplo 117

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrílico (660 mg), N,N'-carbonildiimidazol (404 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron 3-metilbutan-1-sulfonamida (301 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (380 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]acrilamida (320 mg, rendimiento: 36%) en forma de cristales incoloros. Punto de fusión 143-144°C.

Ejemplo 118

Una mezcla de ácido (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}acrílico (660 mg), N,N'-carbonildiimidazol (426 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 1 hora, se agregaron 3-metilbutan-1-sulfonamida (318

mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (401 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}-N-[(3-metilbutil)sulfonil]acrilamida (480 mg, rendimiento: 54%) en forma de cristales incoloros. Punto de fusión 145-147°C.

Ejemplo 119

Una mezcla de ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrílico (300 mg), N,N'-carbonildiimidazol (182 mg) y N,N-dimetilformamida (8.0 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron 3-metoxipropano-1-sulfonamida (138 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (171 mg), y la mezcla se agitó a 100°C durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo

se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]-N-[(3-metoxipropil)sulfonil]acrilamida (260 mg, rendimiento: 65%) en forma de cristales incoloros. Punto de fusión 137-138°C.

Ejemplo 120

Una mezcla de ácido 3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]propanoico (430 mg), N,N'-carbonildiimidazol (260 mg) y tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metoxipropano-1-sulfonamida (197 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (244 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]-N-[(3-metoxipropil)sulfonil]propanamida (390 mg, rendimiento: 68%) en forma de cristales incoloros. Punto de

fusión 152-154ºC.

Ejemplo 121

Una mezcla de ácido (2E)-3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (840 mg), N,N'-carbonildiimidazol (528 mg) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante 1 hora, se añadieron pentan-1-sulfonamida (345 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (497 mg), y la mezcla se agitó a 100ºC durante 15 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)acrilamida (400 mg, rendimiento: 35%) en forma de cristales incoloros. Punto de fusión 147-148ºC.

Ejemplo 122

Una mezcla de ácido 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoico (700 mg), N,N'-carbonildiimidazol (408 mg) y tetrahidrofurano (15 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida

(286 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (412 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (500 mg, rendimiento: 53%) en forma de cristales incoloros. Punto de fusión 136-137°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.90 (3 H, t, J = 7.1 Hz), 1.23 - 1.47 (13 H, m), 1.70 - 1.85 (2 H, m), 2.57 - 2.68 (2 H, m), 2.77 - 2.87 (2 H, m), 3.34 - 3.43 (2 H, m), 5.39 (2 H, s), 5.99 (1 H, s), 6.50 (1 H, d, J = 8.1 Hz), 7.42 (1 H, d, J = 8.1 Hz), 7.65 (1 H, s), 8.00 (1 H, brs).

Ejemplo 123

Una mezcla de ácido 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}propanoico (500 mg), N,N'-carbonildiimidazol (313 mg) y tetrahidrofurano (15 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 3-metoxipropano-1-sulfonamida (237 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (296 mg). La mezcla se agitó a temperatura ambiente durante 15 h y

se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 7:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar 3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-[(3-metoxipropil)sulfonil]propanamida (370 mg, rendimiento: 55%) en forma de cristales incoloros. Punto de fusión 149-150°C.

Ejemplo 124

Bajo enfriamiento con hielo, a una solución de {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (1.89 g) en N,N-dimetilformamida (20 ml) se añadió hidruro de sodio (60% en aceite, 479 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se sumergió en un baño de hielo, se añadió 1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-carbaldehído (1.00 g), y la mezcla se agitó durante 1 hora. La mezcla de reacción se vertió en salmuera saturada, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({(E)-2-[1-(2,4-

diclorobencil)-3-isopropoxi-1H-pirazol-5-il]vinil}sulfonil)carbamato de ter-butilo (610 mg, rendimiento: 39%) en forma de cristales incoloros. Punto de fusión 152-153°C.

Ejemplo 125

Una mezcla de ácido hexanoico (107 mg), N,N'-carbonildiimidazol (299 mg) y tetrahidrofurano (6 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron (E)-2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etilensulfonamida (300 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (305 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar N-({(E)-2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]vinil}sulfonil)hexanamida (110 mg, rendimiento: 29%) en forma de cristales incoloros. Punto de fusión 73-75°C.

Ejemplo 126

Una mezcla de ácido hexanoico (98 mg), N,N'-carbonildiimidazol (273 mg) y tetrahidrofurano (4 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta

temperatura ambiente, se añadieron 2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etansulfonamida (220 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (256 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se concentró. Se añadió ácido clorhídrico 1 N al concentrado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar N-({2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etil}sulfonil)hexanamida (25 mg, rendimiento: 9%) en forma de cristales incoloros. Punto de fusión 107-108°C.

Ejemplo 127

Bajo enfriamiento con hielo, a una solución de {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (7.24 g) en N,N-dimetilformamida (120 ml) se añadió hidruro de sodio (60% en aceite, 479 mg), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió con un baño de hielo, se añadió 3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-carbaldehído (4.00 g), y la mezcla se agitó durante 1 hora. La mezcla de reacción se vertió en salmuera saturada, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía

en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({(E)-2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]vinil}sulfonil)carbamato de ter-butilo (610 mg, rendimiento: 39%) en forma de cristales incoloros. Punto de fusión 152-153°C.

Ejemplo 128

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (500 mg), 4-pirrolidinopiridina (182 mg) y piridina (10 ml) se añadió cloruro de hexanoilo (497 mg), y la mezcla se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se vertió en ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, solución acuosa saturada de carbonato ácido de sodio, salmuera saturada, se secó ($MgSO_4$) y se concentró. A una mezcla del residuo, 4-dimetilaminopiridina (299 mg), N,N-diisopropiletilamina (318 mg), y N,N-dimetilacetamida (10 ml) se añadió cloruro de hexanoilo (331 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se vertió en agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 -

3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar N-({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)hexanamida (250 mg, rendimiento: 40%) en forma de cristales incoloros. Punto de fusión 90-92°C.

Ejemplo 129

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (500 mg), 4-dimetilaminopiridina (299 mg), N,N-diisopropiletilamina (318 mg) y N,N-dimetilacetamida (10 ml) se añadió cloroformiato de butilo (336 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de butilo (420 mg, rendimiento: 67%) en forma de cristales incoloros. Punto de fusión 108-111°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.94 (3 H, t, J = 7.2 Hz), 0.95 (3 H, t, J = 7.2 Hz), 1.30 - 1.80 (8 H, m), 2.97 - 3.07 (2 H, m), 3.58 - 3.68 (2 H, m), 4.08 (2 H, t, J = 6.6 Hz), 4.17 (2 H, t, J = 6.6 Hz), 5.18 (2 H, s), 5.60 (1 H, s), 6.61

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(1 H, d, J = 8.3 Hz), 7.16 (1 H, dd, J = 8.3, 2.1 Hz), 7.39 (1 H, d, J = 2.1 Hz).

Ejemplo 130

Bajo enfriamiento con hielo, a una mezcla de (E)-2-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]etilensulfonamida (1.00 g), 4-dimetilaminopiridina (604 mg), N,N-diisopropiletilamina (640 mg) y N,N-dimetilacetamida (20 ml) se añadió cloroformiato de butilo (676 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:24 - 1:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({(E)-2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]vinil}sulfonil)carbamato de butilo (470 mg, rendimiento: 38%) en forma de cristales incoloros. Punto de fusión 137-138°C.

Ejemplo 131

Bajo enfriamiento con hielo, a una mezcla de (E)-2-[1-(2,4-diclorobencil)-3-butoxi-1H-pirazol-5-il]etilensulfonamida (1.00 g), 4-dimetilaminopiridina (604 mg), N,N-diisopropiletilamina (640 mg) y N,N-dimetilacetamida (20 ml) se añadió cloruro de hexanoilo (666 mg), y la mezcla

se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar N-({(E)-2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]vinil}sulfonil)hexanamida (830 mg, rendimiento: 67%) en forma de cristales incoloros. Punto de fusión 117-119°C.

Ejemplo 132

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió cloroformiato de propilo (181 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-

il]etil}sulfonil)carbamato de propilo (250 mg, rendimiento: 69%) en forma de cristales incoloros. Punto de fusión 92-94°C.

Ejemplo 133

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió isocloroformiato de butilo (202 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de isobutilo (280 mg, rendimiento: 75%) en forma de cristales incoloros. Punto de fusión 114-116°C.

Ejemplo 134

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió cloroformiato de 2-metoxietilo (205 mg), y la mezcla se

agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de 2-metoxietilo (280 mg, rendimiento: 75%) en forma de cristales incoloros. Punto de fusión 82-86°C.

Ejemplo 135

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió cloroformiato de pentilo (223 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-

il]etil}sulfonil)carbamato de pentilo (250 mg, rendimiento: 65%) en forma de cristales incoloros. Punto de fusión 91-93°C.

Ejemplo 136

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió cloroformiato de bencilo (252 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:19 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de bencilo (130 mg, rendimiento: 33%) en forma de cristales incoloros. Punto de fusión 99-101°C.

Ejemplo 137

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió cloroformiato de alilo (178 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se

concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de alilo (200 mg, rendimiento: 55%) en forma de cristales incoloros. Punto de fusión 94-95°C.

Ejemplo 138

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió cloroformiato de hexilo (178 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de bencilo (160 mg, rendimiento: 41%) en forma de cristales incoloros. Punto de fusión 92-95°C.

Ejemplo 139

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió isocloroformiato de propilo (181 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de isopropilo (240 mg, rendimiento: 66%) en forma de cristales incoloros. Punto de fusión 120-121°C.

Ejemplo 140

Bajo enfriamiento con hielo, a una mezcla de 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etansulfonamida (300 mg), 4-dimetilaminopiridina (181 mg), N,N-diisopropiletilamina (191 mg) y N,N-dimetilacetamida (5 ml) se añadió 2.2-dimetilcloroformiato de propilo (223 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al

residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:24 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de 2.2-dimetilpropilo (150 mg, rendimiento: 39%) en forma de cristales incoloros. Punto de fusión 116-118°C.

Ejemplo 141

Bajo enfriamiento con hielo, a una mezcla de 3-metilbutano-1-sulfonamida (230 mg), piridina (156 mg) y tolueno (10 ml) se añadió trifosgeno (226 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se sumergió en un baño de hielo, se añadieron [1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]metanol (400 mg), N,N-diisopropiletilamina (821 mg), 4-dimetilaminopiridina (155 mg) y tetrahidrofurano (10 ml), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano

para dar [(3-metilbutil)sulfonil]carbamato de [1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]metilo (210 mg, rendimiento: 34%) en forma de cristales incoloros. Punto de fusión 104-107°C.

Ejemplo 142

Bajo enfriamiento con hielo, a una mezcla de pentan-1-sulfonamida (289 mg), piridina (196 mg) y tolueno (10 ml) se añadió trifosgeno (283 mg), y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se sumergió en un baño de hielo, se añadieron [1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]metanol (500 mg), N,N-diisopropiletilamina (1.03 g), 4-dimetilaminopiridina (194 mg) y tetrahidrofurano (10 ml), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se añadió ácido clorhídrico 1 N al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (pentilsulfonil)carbamato de [1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]metilo (150 mg, rendimiento: 19%) en forma de cristales incoloros. Punto de fusión 126-128°C.

Ejemplo 143

A una solución de 3-{1-[2-cloro-4-

(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il)propiónico (502 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (310 mg), y la mezcla se calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (201 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 7 h. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-isopropoxi-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (39 mg, rendimiento: 6%) en forma de cristales blancos. Punto de fusión 147.0-149.0°C.

Ejemplo 144

A una solución de 3-[3-isopropoxi-1-(piridin-2-ilmetil)-1H-pirazol-5-il]propionato de etilo (1.09 g) en tetrahidrofurano (3.5 ml) y etanol (3.5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (7.5 ml), y la mezcla se agitó a 50°C durante 1 hora. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (7.5

ml), se concentró y el residuo se disolvió en acetato de etilo. La capa orgánica se lavó dos veces con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco.

A una solución de el sólido obtenido en tetrahidrofurano (8 ml) se añadió N,N'-carbonildiimidazol (167 mg), y la mezcla se calentó a reflujo durante 1.5 h. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (115 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.25 ml) a la mezcla de reacción, y la mezcla se agitó durante 4 h. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 4:1, v/v) para dar una 3-[3-isopropoxi-1-(piridin-2-ilmetil)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida (45 mg, rendimiento: 15%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.84 - 0.94 (3 H, m), 1.24 (6 H, d, J = 6.2 Hz), 1.27 - 1.45 (4 H, m), 1.64 - 1.81 (2 H, m), 2.66 (2 H, t, J = 7.1 Hz), 3.07 (2 H, t, J = 7.1 Hz), 3.16 - 3.27 (2 H, m), 4.50 - 4.65 (1 H, m), 5.16 (2 H, s), 5.48 (1 H, s), 7.30 - 7.38 (1 H, m), 7.43 (1 H, d, J = 7.7 Hz), 7.75 -

7.85 (1 H, m), 8.70 (1 H, d, J = 4.1 Hz).

Ejemplo 145

A una solución de ácido [3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]acético (501 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (322 mg), y la mezcla se calentó a reflujo durante 50 min. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (215 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar una 2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)acetamida (171 mg, rendimiento: 25%) en forma de un sólido de color anaranjado pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.81 - 1.08 (6 H, m), 1.23 - 1.90 (10 H, m), 3.25 - 3.36 (2 H, m), 3.60 (2 H, s), 4.11 (2 H, t, J = 6.6 Hz), 5.20 (2 H, s), 5.74 (1 H, s), 6.75 (1 H, d, J = 8.3 Hz), 7.19 (1 H, dd, J = 8.4, 2.0 Hz), 7.39 (1 H, d, J = 2.1 Hz).

Ejemplo 146

A una solución de ácido 4-[3-butoxi-1-(2,4-

diclorobencil)-1H-pirazol-5-il]butanoico (1.36 g) en tetrahidrofurano (15 ml) se añadió N,N'-carbonildiimidazol (891 mg), y la mezcla se calentó a reflujo durante 1 hora 20 min. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (645 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.80 ml) a la mezcla de reacción, y la mezcla se agitó durante 6 h. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 4-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)butanamida (989 mg, rendimiento: 54%) en forma de cristales blancos. Punto de fusión 121.0-122.0°C.

Ejemplo 147

A una solución de ácido 5-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]pentanoico (433 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (312 mg), y la mezcla se calentó a reflujo durante 30 min. Tras enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (205 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.25 ml) a la mezcla de reacción, y la mezcla se agitó

durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con solución acuosa saturada de cloruro de amonio, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 5-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)pentanamida (290 mg, rendimiento: 50%) en forma de cristales blancos. Punto de fusión 91-93°C.

Ejemplo 148

Una solución de ácido 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]propanoico (0.50 g) y N,N'-carbonildiimidazol (0.25 g) en tetrahidrofurano (10 ml) se agitó con calentamiento a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron metansulfonamida (0.15 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.24 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadieron ácido clorhídrico 1 N (8 ml) y salmuera (10 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (20 mlx2). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con

acetato de etilo-hexano (3:1, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 3-[1-(2,4-diclorobencil)-3-isopropoxi-1H-pirazol-5-il]-N-(metilsulfonil)propanamida (0.53 g, rendimiento: 86%) en forma de cristales incoloros. Punto de fusión 104-105°C.

Ejemplo 149

Una solución de (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(2-metoxietoxi)-1H-pirazol-5-il]acrílico (405 mg) y N,N'-carbonildiimidazol (195 mg) en N,N-dimetilformamida (4 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron pentan-1-sulfonamida (181 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.179 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción para ajustar el pH a aproximadamente 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 2:3, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(2-metoxietoxi)-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (278 mg, rendimiento: 52%) en forma

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de cristales incoloros. Punto de fusión 130.5-132.5°C.

Ejemplo 150

Una solución de ácido (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}acrílico (500 mg) y N,N'-carbonildiimidazol (250 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron 3-metilbutano-1-sulfonamida (233 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.232 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 2:3, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-{3-butoxi-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-[(3-metilbutil)sulfonil]acrilamida (304 mg, rendimiento: 57%) en forma de cristales incoloros. Punto de fusión 89.5-90.5°C.

Ejemplo 151

Una solución de ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]acrílico (500 mg) y N,N'-carbonildiimidazol (250 mg) en

N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron pentan-1-sulfonamida (233 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.232 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 2:3, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(ciclopropilmetoxi)-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (345 mg, rendimiento: 65%) en forma de cristales incoloros. Punto de fusión 148-151°C.

Ejemplo 152

Una solución de (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(2-metoxietoxi)-1H-pirazol-5-il]acrílico (500 mg) y N,N'-carbonildiimidazol (240 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron 3-metilbutano-1-sulfonamida (224 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.222 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido

clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 2:3, v/v) y se concentró. Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano. Se añadió éter diisopropílico a los cristales crudos obtenidos, y la mezcla se agitó durante 1 hora, y se recristalizó en metanol-agua para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(2-metoxietoxi)-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]acrilamida (292 mg, rendimiento: 54%) en forma de cristales incoloros. Punto de fusión 114-116°C.

Ejemplo 153

Una solución de ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrílico (535 mg) y N,N'-carbonildiimidazol (221 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron 3-metilbutano-1-sulfonamida (206 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.203 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se

añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:10 - 1:2, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]-N-[(3-metilbutil)sulfonil]acrilamida (315 mg, rendimiento: 45%) en forma de cristales incoloros. Punto de fusión 149.5-152.5°C.

Ejemplo 154

Una solución de ácido (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]acrílico (535 mg) y N,N'-carbonildiimidazol (221 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron pentan-1-sulfonamida (206 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.203 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de

gel de sílice, y se eluyó con acetato de etilo-hexano (1:10 - 1:2, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[1-[2-cloro-4-(trifluorometil)bencil]-3-(tetrahidro-2H-piran-4-iloxi)-1H-pirazol-5-il]-N-(pentilsulfonil)acrilamida (337 mg, rendimiento: 48%) en forma de cristales incoloros. Punto de fusión 160.5-161°C.

Ejemplo 155

Una solución de (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}acrílico (501 mg) y N,N'-carbonildiimidazol (242 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron pentan-1-sulfonamida (225 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.223 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:20 - 1:2, v/v), se concentró y los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}-N-

(pentilsulfonil)acrilamida (313 mg, rendimiento: 46%) en forma de cristales incoloros. Punto de fusión 139-140.5°C.

Ejemplo 156

Una solución de ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}propanoico (450 mg) y N,N'-carbonildiimidazol (216 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron pentan-1-sulfonamida (201 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.199 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:20 - 1:2, v/v) y se concentró. Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano. Los cristales crudos obtenidos se purificaron por HPLC (acetonitrilo:agua, con contenido de 0.01% de TFA, 40:60 - 100:0, v/v), y se recristalizó en acetato de etilo-hexano para dar 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida (261 mg, rendimiento: 43%) en forma de cristales incoloros. Punto de fusión 151.5-153.5°C.

Ejemplo 157

Una solución de ácido 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}propanoico (450 mg) y N,N'-carbonildiimidazol (216 mg) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 1 hora. Se añadieron 3-metilbutan-1-sulfonamida (201 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.199 ml), y la mezcla se agitó a 100°C durante 12 h. Tras enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se ajustó a aproximadamente pH 4. Se añadió agua a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:20 - 1:2, v/v) y se concentró. Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano. Los cristales crudos obtenidos se purificaron por HPLC (acetonitrilo:agua, con contenido de 0.01% de TFA, 40:60 - 100:0, v/v), y se recristalizó en acetato de etilo-hexano para dar 3-{1-[2-cloro-4-(trifluorometil)bencil]-3-ciclopropil-1H-pirazol-5-il}-N-[(3-metilbutil)sulfonil]propanamida (191 mg, rendimiento: 31%) en forma de cristales incoloros. Punto de fusión 160.5-162.5°C.

Ejemplo 158

A una solución (10 ml) de ácido (2E)-3-[2-

(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]acrílico (0.86 g) en acetonitrilo, se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.74 g), 4-dimetilaminopiridina (0.47 g) y pentan-1-sulfonamida (0.43 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró, se vertió agua en el residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (0.30 g, rendimiento: 25%) en forma de cristales incoloros. Punto de fusión 97.5-98.3°C.

Ejemplo 159

Una solución de (2E)-3-[2-(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (165 mg) y paladio sobre carbón al 10% (40 mg) en metanol (20 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 3-[2-

(ciclohexilmetoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (151 mg, rendimiento: 91%) en forma de cristales incoloros. Punto de fusión 81.0-82.0°C.

Ejemplo 160

A una solución de ácido (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]acrílico (400 mg) en tetrahidrofurano (8 ml) se añadió N,N'-carbonildiimidazol (338 mg), y la mezcla se calentó a reflujo durante 30 min. Tras enfriar hasta temperatura ambiente, se añadieron 1.8-diazabiciclo[5.4,0]-7-undecene (310 mg) y pentan-1-sulfonamida (215 mg) a la mezcla de reacción, y la mezcla se agitó a 60°C durante 100 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (147 mg, rendimiento: 25%) en forma de cristales incoloros. Punto de fusión 64.8-66.3°C.

Ejemplo 161

A una solución mixta de ácido (2E)-3-[2-{[1-(terbutoxicarbonil)piperidin-4-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (558 mg) en acetonitrilo (8 ml) y N,N-dimetilformamida (5 ml) se añadieron clorhidrato de 1-

etil-3-(3-dimetilaminopropil)carbodiimida (334 mg), 4-dimetilaminopiridina (246 mg) y pentan-1-sulfonamida (232 mg), y la mezcla se agitó a temperatura ambiente durante 5 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:2, v/v) para dar 4-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)piperidin-1-carboxilato de ter-butilo (177 mg, rendimiento: 24%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.2 Hz), 1.25 - 1.47 (4 H, m), 1.47 (9 H, s), 1.83 - 1.86 (4 H, m), 1.92 - 2.00 (2 H, m), 3.26 - 3.32 (2 H, m), 3.45 (3 H, s), 3.46 - 3.54 (2 H, m), 3.74 - 3.79 (4 H, m), 4.13 - 4.16 (2 H, m), 4.47 - 4.53 (1 H, m), 6.43 (1 H, d, J = 15.6 Hz), 6.51 - 6.52 (2 H, m), 7.41 - 7.44 (1 H, m), 7.95 (1 H, d, J = 15.6 Hz), 8.12 (1 H, brs).

Ejemplo 162

Una solución de 4-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)piperidin-1-carboxilato de ter-butilo (181 mg) y paladio sobre carbón al 10% (40 mg) en metanol (20 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. El catalizador

se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar 4-(5-(2-metoxietoxi)-2-{3-oxo-3-[(pentilsulfonil)amino]propil}fenoxi)piperidin-1-carboxilato de ter-butilo (147 mg) en forma de un sólido amorfo incoloro. A una solución del sólido amorfo incoloro obtenido en acetato de etilo (4 ml) se añadió una solución en acetato de etilo de cloruro de hidrógeno 4 N (2 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró y se secó para dar (2E)-3-[4-(2-metoxietoxi)-2-(piperidin-4-iloxi)fenil]-N-(pentilsulfonil)acrilamida (123 mg, rendimiento: 94%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:0.84 (3 H, t, J = 7.1 Hz), 1.23 - 1.31 (4 H, m), 1.50 - 1.60 (2 H, m), 1.79 - 1.90 (2 H, m), 2.02 - 2.13 (2 H, m), 2.48 - 2.50 (2 H, m), 2.70 - 2.75 (2 H, m), 3.10 - 3.18 (4 H, m), 3.27 - 3.29 (2 H, m), 3.29 (3 H, s), 3.62 - 3.64 (2 H, m), 4.02 - 4.05 (2 H, m), 4.65 - 4.70 (1 H, m), 6.45 (1 H, d, J = 8.2 Hz), 6.61 (1 H, s), 7.02 (1 H, d, J = 8.2 Hz), 8.73 (2 H, brs), 11.61 (1 H, brs).

Ejemplo 163

A una solución de ácido (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]acrílico (517 mg) en tetrahidrofurano (10 ml) se añadió N,N'-carbonildiimidazol (392 mg), y la mezcla se

calentó a reflujo durante 1 h. Tras enfriar hasta temperatura ambiente, se añadieron 1.8-diazabiciclo[5.4,0]-7-undecene (386 mg), 4-dimetilaminopiridina (238 mg) y pentan-1-sulfonamida (374 mg) a la mezcla de reacción, y la mezcla se calentó a reflujo durante 22 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (321 mg, rendimiento: 44%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.1 Hz), 1.31 - 1.45 (6 H, m), 1.52 - 1.65 (4 H, m), 1.78 - 1.90 (4 H, m), 1.97 - 2.05 (2 H, m), 3.46 (3 H, s), 3.48 - 3.55 (2 H, m), 3.76 - 3.77 (2 H, m), 4.13 - 4.16 (2 H, m), 4.26 - 4.35 (1 H, m), 6.45 - 6.53 (3 H, m), 7.40 (1 H, d, J = 8.4 Hz), 7.70 (1 H, brs), 7.94 (1 H, d, J = 15.6 Hz).

Ejemplo 164

Una solución de (2E)-3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (238 mg) y paladio sobre carbón al 10% (40 mg) en metanol (20 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en

columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7, v/v) para dar 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (246 mg, rendimiento: 99%) en forma de cristales incoloros. Punto de fusión 64.1-65.4°C.

Ejemplo 165

A una solución de ácido (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]acrílico (500 mg) en acetonitrilo (5 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (533 mg), trietilamina (495 mg), 4-dimetilaminopiridina (189 mg) y pentan-1-sulfonamida (239 mg), y la mezcla se agitó a temperatura ambiente durante 28 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]-N-(pentilsulfonil)acrilamida (489 mg, rendimiento: 69%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.1 Hz), 1.26 - 1.48 (4 H, m), 1.71 - 2.20 (6 H, m), 3.45 (3 H, s), 3.45 - 3.54 (2 H, m), 3.74 - 3.77 (2 H, m), 3.85 - 4.02 (4 H, m), 4.11 - 4.16 (2 H, m), 4.35 - 4.42 (1 H, m), 6.52 - 6.54 (2

H, m), 6.61 (1 H, d, J = 15.6 Hz), 7.38 (1 H, d, J = 8.1 Hz), 7.85 (1 H, d, J = 15.6 Hz), 8.56 (1 H, brs).

Ejemplo 166

Una solución de (2E)-3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]-N-(pentilsulfonil)acrilamida (319 mg) y paladio sobre carbón al 10% (40 mg) en metanol (20 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]-N-(pentilsulfonil)propanamida (296 mg, rendimiento: 92%) en forma de cristales incoloros. Punto de fusión 57.8-58.9°C.

Ejemplo 167

Una solución de (2E)-3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (268 mg) y paladio sobre carbón al 10% (41 mg) en metanol (20 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7, v/v). Los cristales crudos obtenidos se

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recristalizaron en acetato de etilo-hexano para dar 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (230 mg, rendimiento: 85%) en forma de cristales incoloros. Punto de fusión 81.7-82.8°C.

Ejemplo 168

A una solución de ácido (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]acrílico (530 mg) en acetonitrilo (10 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (461 mg), trietilamina (410 mg), 4-dimetilaminopiridina (166 mg) y pentan-1-sulfonamida (203 mg), y la mezcla se agitó a temperatura ambiente durante 40 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (385 mg, rendimiento: 54%) en forma de cristales incoloros. Punto de fusión 137.6-138.2°C.

Ejemplo 169

A una solución mixta de (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]-N-

(pentilsulfonil)acrilamida (210 mg) en metanol (15 ml) y tetrahidrofurano (15 ml) se añadió un complejo de paladio-carbón activado-etilenodiamina (30 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (128 mg, rendimiento: 60%) en forma de cristales incoloros. Punto de fusión 106.7-108.2°C.

Ejemplo 170

A una solución de ácido (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrílico (600 mg) en N,N-dimetilformamida (6 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (407 mg), 4-dimetilaminopiridina (290 mg) y pentan-1-sulfonamida (241 mg), y la mezcla se agitó a temperatura ambiente durante 72 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de

etilo-hexano para dar (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (352 mg, rendimiento: 43%) en forma de cristales incoloros. Punto de fusión 119.0-120.3°C.

Ejemplo 171

A una solución mixta de (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (167 mg) en metanol (10 ml) y tetrahidrofurano (10 ml) se añadió complejo de paladio-carbón activado-etilenodiamina (20 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 7 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (116 mg, rendimiento: 69%) en forma de cristales incoloros. Punto de fusión 92.2-93.6°C.

Ejemplo 172

A una solución de ácido (2E)-3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}acrílico (650 mg) en acetonitrilo (10 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (543 mg), trietilamina (489 mg), 4-dimetilaminopiridina (195 mg) y pentan-1-sulfonamida (242 mg),

y la mezcla se agitó a temperatura ambiente durante 24 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}-N-(pentilsulfonil)acrilamida (780 mg, rendimiento: 91%) como un sólido amorfo.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.87 (3 H, t, J = 7.1 Hz), 1.27 - 1.40 (4 H, m), 1.75 - 1.83 (2 H, m), 2.43 (3 H, s), 3.40 - 3.44 (2 H, m), 3.45 (3 H, s), 3.74 - 3.78 (2 H, m), 4.16 - 4.19 (2 H, m), 5.03 (2 H, s), 6.53 - 6.58 (2 H, m), 6.76 (1 H, d, J = 2.1 Hz), 7.38 - 7.48 (4 H, m), 7.85 - 7.91 (2 H, m), 7.99 - 8.02 (2 H, m).

Ejemplo 173

Una solución de (2E)-3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}-N-(pentilsulfonil)acrilamida (270 mg) y paladio sobre carbón al 10% (40 mg) en metanol (30 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v). Los cristales

crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 3-{4-(2-metoxietoxi)-2-[(5-metil-2-fenil-1.3-oxazol-4-il)metoxi]fenil}-N-(pentilsulfonil)propanamida (240 mg, rendimiento: 88%) en forma de cristales incoloros. Punto de fusión 95.9-96.7°C.

Ejemplo 174

A una solución de ácido (2E)-3-{4-(2-metoxietoxi)-2-[2-nitro-5-(trifluorometil)fenoxi]fenil}acrílico (443 mg) en acetonitrilo (8 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (309 mg), 4-dimetilaminopiridina (164 mg) y pentan-1-sulfonamida (157 mg), y la mezcla se agitó a temperatura ambiente durante 14 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-{4-(2-metoxietoxi)-2-[2-nitro-5-(trifluorometil)fenoxi]fenil}-N-(pentilsulfonil)acrilamida (75 mg, rendimiento: 13%) en forma de cristales incoloros. Punto de fusión 164.5-165.2°C.

Ejemplo 175

A una solución de ácido (2E)-3-[2-[2-cloro-4-(trifluorometil)fenoxi]-4-(2-metoxietoxi)fenil]acrílico (715

mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (502 mg), 4-dimetilaminopiridina (278 mg) y pentan-1-sulfonamida (261 mg), y la mezcla se agitó a temperatura ambiente durante 18 h. Se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-[2-cloro-4-(trifluorometil)fenoxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (285 mg, rendimiento: 30%) en forma de cristales incoloros. Punto de fusión 134.1-135.1°C.

Ejemplo 176

A una solución de ácido (2E)-3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)acrílico (350 mg) en acetonitrilo (6 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (350 mg), trietilamina (283 mg), 4-dimetilaminopiridina (135 mg) y pentan-1-sulfonamida (144 mg), y la mezcla se agitó a temperatura ambiente durante 30 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió

a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)-N-(pentilsulfonil)acrilamida (149 mg, rendimiento: 31%) en forma de cristales amarillos. Punto de fusión 142.3-142.6°C.

Ejemplo 177

Una solución de (2E)-3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)-N-(pentilsulfonil)acrilamida (200 mg) y paladio sobre carbón al 10% (35 mg) en metanol (20 ml) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v) para dar 3-(4-(2-metoxietoxi)-2-{[4-(trifluorometil)fenil]amino}fenil)-N-(pentilsulfonil)propanamida (101 mg, rendimiento: 50%) como un sólido amorfo.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.86 (3 H, t, J = 6.9 Hz), 1.22 - 1.38 (4 H, m), 1.62 - 1.71 (2 H, m), 2.65 (2 H, t, J = 6.5 Hz), 2.88 (2 H, t, J = 6.5 Hz), 3.29 - 3.34 (2 H, m), 3.43 (3 H, s), 3.71 - 3.73 (2 H, m), 4.03 - 4.06 (2 H, m), 6.58 (1 H, s), 6.70 (1 H, dd, J = 8.4, 2.4 Hz), 6.86 (1 H, d, J = 2.4 Hz), 6.92 (2 H, d, J = 8.7 Hz), 7.11 (1 H, d, J = 8.4 Hz),

7.45 (2 H, d, J = 8.7 Hz), 7.84 (1 H, s).

Ejemplo 178

A una solución de ácido (2E)-3-[2-[(5-bromo-1.3-tiazol-2-il)oxi]-4-(2-metoxietoxi)fenil]acrílico (660 mg) en acetonitrilo (10 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (573 mg), trietilamina (497 mg), 4-dimetilaminopiridina (206 mg) y pentan-1-sulfonamida (249 mg), y la mezcla se agitó a temperatura ambiente durante 20 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-[(5-bromo-1.3-tiazol-2-il)metil]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (676 mg, rendimiento: 77%) en forma de cristales amarillos. Punto de fusión 88.5-89.1°C.

Ejemplo 179

A una solución de 4-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)piperidin-1-carboxilato de ter-butilo (1.02 g) en acetato de etilo (12 ml), se añadió una solución en acetato de etilo de cloruro de hidrógeno 4 N (6 ml), y la mezcla se agitó a temperatura

ambiente durante 90 min. La mezcla de reacción se concentró y se secó para dar clorhidrato de (2E)-3-[4-(2-metoxietoxi)-2-(piperidin-4-iloxi)fenil]-N-(pentilsulfonil)acrilamida (859 mg, rendimiento: 95%) en forma de un sólido amorfo de color amarillo pálido.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:0.85 (3 H, t, J = 7.1 Hz), 1.22 - 1.40 (4 H, m), 1.60 - 1.72 (2 H, m), 1.80 - 1.95 (2 H, m), 2.10 - 2.18 (2 H, m), 3.02 - 3.30 (4 H, m), 3.30 (3 H, s), 3.34 - 3.48 (2 H, m), 3.64 - 3.66 (2 H, m), 4.14 - 4.17 (2 H, m), 4.77 - 4.82 (1 H, m), 6.57 (1 H, d, J = 15.6 Hz), 6.66 (1 H, d, J = 8.7 Hz), 6.75 (1 H, s), 7.49 (1 H, d, J = 8.7 Hz), 7.79 (1 H, d, J = 15.6 Hz), 8.62 (1 H, brs), 8.83 (1 H, brs), 11.76 (1 H, s).

Ejemplo 180

A una solución de clorhidrato de (2E)-3-[4-(2-metoxietoxi)-2-(piperidin-4-iloxi)fenil]-N-(pentilsulfonil)acrilamida (175 mg) en piridina (5 ml) se añadieron anhídrido acético (110 mg) y 4-dimetilaminopiridina (45 mg), y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró, se añadió una solución acuosa saturada de cloruro de amonio al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con

acetato de etilo-metanol (19:1, v/v) para dar (2E)-3-[2-[(1-acetilpiperidin-4-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (110 mg, rendimiento: 62%) como un sólido amorfo.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.90 (3 H, t, J = 7.1 Hz), 1.25 - 1.45 (4 H, m), 1.80 - 2.06 (6 H, m), 2.13 (3 H, s), 3.39 - 3.55 (7 H, m), 3.70 - 3.74 (1 H, m), 3.74 - 3.77 (2 H, m), 3.85 - 3.95 (1 H, m), 4.13 - 4.16 (2 H, m), 4.59 - 4.63 (1 H, m), 6.51 - 6.56 (3 H, m), 7.42 (1 H, d, J = 9.3 Hz), 7.91 (1 H, d, J = 15.6 Hz), 8.90 (1 H, brs).

Ejemplo 181

A una solución de clorhidrato de (2E)-3-[4-(2-metoxietoxi)-2-(piperidin-4-iloxi)fenil]-N-(pentilsulfonil)acrilamida (190 mg) en piridina (5 ml) se añadieron cloruro de benzoilo (91 mg) y trietilamina (83 mg), y la mezcla se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se concentró, se añadió una solución acuosa saturada de cloruro de amonio al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (4:1, v/v) para dar (2E)-3-[2-[(1-benzoilpiperidin-4-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (163 mg, rendimiento: 75%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.89 (3 H, t, J = 7.1 Hz), 1.25 - 1.46 (4 H, m), 1.78 - 2.20 (6 H, m), 3.30 - 3.55 (6 H, m), 3.55 - 3.90 (4 H, m), 3.93 - 4.18 (3 H, m), 4.61 - 4.65 (1 H, m), 6.45 - 6.53 (3 H, m), 7.38 - 7.43 (6 H, m), 7.96 (1 H, d, J = 15.9 Hz), 8.54 (1 H, s).

Ejemplo 182

A una solución de (2E)-3-[2-[(5-bromo-1.3-tiazol-2-il)metil]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (260 mg) en 1.2-dimetoxietano (6 ml) se añadieron dihidroxifenilborano (84 mg), una solución acuosa 2 N de carbonato de sodio (0.5 ml) y tetraquis(trifenilfosfina)paladio (0) (56 mg), y la mezcla se calentó a reflujo durante 7 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v) para dar (2E)-3-{4-(2-metoxietoxi)-2-[(5-fenil-1.3-tiazol-2-il)metil]fenil}-N-(pentilsulfonil)acrilamida (135 mg, rendimiento: 52%) en forma de un sólido amorfo de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.87 (3 H, t, J = 7.1 Hz), 1.25 - 1.39 (4 H, m), 1.78 - 1.88 (2 H, m), 3.43 (3 H, s), 3.43 - 3.49 (2 H, m), 3.73 - 3.76 (2 H, m), 4.13 - 4.16 (2 H, m), 6.49 (1 H, d, J = 15.9 Hz), 6.86 - 6.92 (2 H, m), 7.31 -

7.44 (6 H, m), 7.51 (1 H, d, J = 9.0 Hz), 7.86 (1 H, d, J = 15.9 Hz), 8.59 (1 H, s).

Ejemplo 183

A una solución de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)benzaldehído (1.40 g) en ácido acético (7 ml) se añadieron ácido etilmalónico (2.46 g) y pirrolidina (3.73 g), y la mezcla se agitó a 100°C durante 72 h. Se añadieron ácido clorhídrico 1 N (1.5 ml) y agua (14 ml) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 hora. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7, v/v) para dar ácido (2E)-2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)benciliden]butanoico (450 mg) en forma de un aceite marrón. A una solución del aceite obtenido en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (276 mg), trietilamina (275 mg), 4-dimetilaminopiridina (101 mg) y pentan-1-sulfonamida (126 mg), y la mezcla se agitó a temperatura ambiente durante 18 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera

saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)benciliden]-N-(pentilsulfonil)butanamida (63 mg, rendimiento: 3%) en forma de cristales incoloros. Punto de fusión 104.5-105.6°C.

Ejemplo 184

A una solución de ácido (2E)-3-[2-{[2-cloro-4-(trifluorometil)fenil]amino}-4-(2-metoxietoxi)fenil]acrílico (487 mg) en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (449 mg), trietilamina (370 mg), 4-dimetilaminopiridina (144 mg) y pentan-1-sulfonamida (177 mg), y la mezcla se agitó a temperatura ambiente durante 22 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-{[2-cloro-4-(trifluorometil)fenil]amino}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (255 mg, rendimiento: 39%) en forma de cristales amarillos. Punto de

fusión 173.5-174.8°C.

Ejemplo 185

A una solución mixta de (2E)-3-{4-(2-metoxietoxi)-2-[(3-metil-5-nitropiridin-2-il)oxi]fenil}acrilato de etilo (630 mg) en tetrahidrofurano (8 ml) y etanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (3.5 ml), y la mezcla se agitó a 60°C durante 1 hora. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se recristalizó en etanol-hexano para dar ácido (2E)-3-{4-(2-metoxietoxi)-2-[(3-metil-5-nitropiridin-2-il)oxi]fenil}acrílico (383 mg) en forma de cristales de color amarillo pálido. Los cristales obtenidos se disolvieron en acetonitrilo (10 ml), y se añadieron anhídrido 2-metil-6-nitrobenzoico (411 mg), trietilamina (305 mg), 4-dimetilaminopiridina (126 mg) y pentan-1-sulfonamida (156 mg), y la mezcla se agitó a temperatura ambiente durante 24 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos

obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-{4-(2-metoxietoxi)-2-[(3-metil-5-nitropiridin-2-il)oxi]fenil}-N-(pentilsulfonil)acrilamida (178 mg, rendimiento: 35%) en forma de cristales incoloros. Punto de fusión 148.0-150.3°C.

Ejemplo 186

A una solución mixta de (2E)-3-(4-(2-metoxietoxi)-2-{[6-(trifluorometil)piridazin-3-il]oxi}fenil)acrilato de etilo (483 mg) en tetrahidrofurano (12 ml) y etanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (2.5 ml), y la mezcla se agitó a temperatura ambiente durante 5 h. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró para dar ácido (2E)-3-(4-(2-metoxietoxi)-2-{[6-(trifluorometil)piridazin-3-il]oxi}fenil)acrílico (353 mg) en forma de cristales incoloros. Los cristales obtenidos se disolvieron en acetonitrilo (10 ml), se añadieron anhídrido 2-metil-6-nitrobenzoico (377 mg), trietilamina (280 mg), 4-dimetilaminopiridina (113 mg) y pentan-1-sulfonamida (139 mg), y la mezcla se agitó a temperatura ambiente durante 24 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de

etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3, v/v) para dar (2E)-3-(4-(2-metoxietoxi)-2-{[6-(trifluorometil)piridazin-3-il]oxi}fenil)-N-(pentilsulfonil)acrilamida (120 mg, rendimiento: 20%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.87 (3 H, t, J = 7.1 Hz), 1.25 - 1.42 (4 H, m), 1.75 - 1.84 (2 H, m), 3.37 - 3.42 (2 H, m), 3.43 (3 H, s), 3.72 - 3.75 (2 H, m), 4.12 - 4.15 (2 H, m), 6.32 (1 H, d, J = 15.6 Hz), 6.77 (1 H, d, J = 2.4 Hz), 6.89 (1 H, dd, J = 9.0, 2.4 Hz), 7.45 (1 H, d, J = 9.0 Hz), 7.54 (1 H, d, J = 9.0 Hz), 7.76 (1 H, d, J = 15.6 Hz), 7.88 (1 H, d, J = 9.0 Hz), 8.32 (1 H, s).

Ejemplo 187

A una solución de ácido (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-2-metilacrílico (358 mg) en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (324 mg), trietilamina (275 mg), 4-dimetilaminopiridina (113 mg) y pentan-1-sulfonamida (138 mg), y la mezcla se agitó a temperatura ambiente durante 20 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo

se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-2-metil-N-(pentilsulfonil)acrilamida (421 mg, rendimiento: 88%) en forma de cristales amarillos. Punto de fusión 97.0-98.0°C.

Ejemplo 188

A una solución de ácido (2E)-2-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benciliden]butanoico (325 mg) en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (332 mg), trietilamina (247 mg), 4-dimetilaminopiridina (98 mg) y pentan-1-sulfonamida (130 mg), y la mezcla se agitó a temperatura ambiente durante 44 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-2-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)benciliden]-N-(pentilsulfonil)butanamida (363 mg, rendimiento: 84%) en forma de cristales incoloros. Punto de fusión 118.0-118.4°C.

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Ejemplo 189

A una solución de ácido (2E)-3-[2-[(2,4-diclorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrílico (304 mg) en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (359 mg), trietilamina (235 mg), 4-dimetilaminopiridina (99 mg) y pentan-1-sulfonamida (136 mg), y la mezcla se agitó a temperatura ambiente durante 20 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 2,4-dicloro-N-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenil)benzamida (160 mg, rendimiento: 40%) en forma de cristales incoloros. Punto de fusión 176.8-177.1°C.

Ejemplo 190

A una solución de ácido (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(3-metoxipropoxi)fenil]-2-metilacrílico (338 mg) en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (312 mg), trietilamina (265 mg), 4-dimetilaminopiridina (100 mg) y pentan-1-sulfonamida (130 mg), y la mezcla se agitó a temperatura ambiente durante

20 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(3-metoxipropoxi)fenil]-2-metil-N-(pentilsulfonil)acrilamida (394 mg, rendimiento: 84%) en forma de cristales amarillos. Punto de fusión 116.0-116.8°C.

Ejemplo 191

A una solución de (2E)-3-[2-[(2,4-difluorobenzoil)amino]-4-(2-metoxietoxi)fenil]acrílico (366 mg) en acetonitrilo (10 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (369 mg), trietilamina (340 mg), 4-dimetilaminopiridina (120 mg) y pentan-1-sulfonamida (157 mg), y la mezcla se agitó a temperatura ambiente durante 24 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para

dar 2,4-difluoro-N-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenil)benzamida (158 mg, rendimiento: 32%) en forma de cristales incoloros. Punto de fusión 140.0-140.8°C.

Ejemplo 192

A una solución de ácido (2E)-3-{2-({5-[(ter-butoxicarbonil)amino]-3-metilpiridin-2-il}oxi)-4-(2-metoxietoxi)fenil]acrílico (256 mg) en acetonitrilo (8 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (244 mg), trietilamina (180 mg), 4-dimetilaminopiridina (76 mg) y pentan-1-sulfonamida (99 mg), y la mezcla se agitó a temperatura ambiente durante 22 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar [6-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)-5-metilpiridin-3-il]carbamato de ter-butilo (288 mg, rendimiento: 86%) en forma de cristales amarillos. Punto de fusión 149.5-150.2°C.

Ejemplo 193

A una solución de ácido (2E)-3-(2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)acrílico (7.90 g) en acetonitrilo (30 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (3.51 g), 4-dimetilaminopiridina (2.59 g) y 1-pentanesulfonamida (2.19 g), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:4, v/v) para dar una (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)-N-(pentilsulfonil)acrilamida (4.50 g, rendimiento: 46%) en forma de un sólido blanco. La recristalización en éter diisopropílico-hexano dio un polvo blanco. Punto de fusión 106-108°C.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.89 (3 H, t, J = 7.2 Hz), 0.98 - 1.17 (21 H, m), 1.21 - 1.49 (4 H, m), 1.70 - 1.92 (2 H, m), 3.35 - 3.56 (2 H, m), 3.91 - 4.19 (4 H, m), 6.37 (1 H, d, J = 15.8 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.90 (1 H, dd, J = 8.7, 2.5 Hz), 7.60 (1 H, d, J = 8.9 Hz), 7.72 - 7.83 (2 H, m), 8.03 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.0, 0.9 Hz).

Ejemplo 194

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxietoxi)fenil]-N-(pentilsulfonil)acrilamida (252 mg) en piridina (2 ml) se añadió anhídrido acético (0.088 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar 2-(3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)acetato de etilo (237 mg, rendimiento: 87%) en forma de cristales blancos. Punto de fusión 141-144°C.

Ejemplo 195

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]acrílico (0.79 g) en acetonitrilo (6 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (541 mg), 4-dimetilaminopiridina (398 mg) y pentan-1-sulfonamida (269 mg), y la mezcla se agitó a temperatura ambiente durante 16 h. Se

añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:4, v/v) para dar un sólido blanco. La recristalización en éter dietílico-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]-N-(pentilsulfonil)acrilamida (202 mg, rendimiento: 20%) en forma de un polvo blanco. Punto de fusión 126.5-128.5°C.

Ejemplo 196

A una solución de ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(1,3-dioxolan-2-il)etoxi]fenil}acrílico (1.00 g) en acetonitrilo (6 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (541 mg), 4-dimetilaminopiridina (398 mg) y pentan-1-sulfonamida (328 mg), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se

sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:4, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(1,3-dioxolan-2-il)etoxi]fenil}-N-(pentilsulfonil)acrilamida (194 mg, rendimiento: 15%) en forma de un polvo blanco. Punto de fusión 116-118°C.

Ejemplo 197

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(pirimidin-2-iloxi)fenil]acrílico (1.00 g) en acetonitrilo (12 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (782 mg), 4-dimetilaminopiridina (374 mg) y pentan-1-sulfonamida (295 mg), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:2, v/v) para dar un sólido blanco. La recristalización en éter dietílico-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(pirimidin-2-iloxi)fenil]-N-(pentilsulfonil)acrilamida (140

mg, rendimiento: 12%) en forma de un polvo blanco. Punto de fusión 80.5-82.5°C.

Ejemplo 198

A una solución de ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}acrílico (831 mg) en acetonitrilo (12 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (652 mg), 4-dimetilaminopiridina (312 mg) y pentan-1-sulfonamida (257 mg), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:20 - 1:4, v/v) para dar un sólido blanco. La recristalización en éter diisopropílico-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}-N-(pentilsulfonil)acrilamida (397 mg, rendimiento: 38%) en forma de un polvo blanco. Punto de fusión 83-85.5°C.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.26 - 1.44 (7 H, m), 1.46 - 1.70 (4 H, m), 1.70 - 2.04 (4 H, m), 3.45 (3 H, s), 3.73 - 3.76 (2 H, m), 4.11 - 4.14 (2 H, m), 4.20 - 4.32 (3 H, m),

6.38 - 6.52 (3 H, m), 7.42 (1 H, d, J = 8.7 Hz), 7.93 (1 H, d, J = 16.2 Hz).

La recristalización de los cristales crudos obtenidos en las mismas condiciones que en el Ejemplo 198 del éter dietílico-hexano dio cristales. El patrón de difracción de polvos por rayos X de este cristal tal como se midió usando rayo de Cu-Kα (voltaje del tubo: 40 KV; corriente del tubo: 50 mA) como una fuente de radiación y RINT2100 tipo Ultima+ (Rigaku Corporation) se muestra en la Fig. 3.

Datos (pico principal) de la difracción de polvos por rayos X

Ángulo de difracción: 2θ (°)	Espaciado: valor d (angstrom)
4.20	21.0
6.92	12.8
11.3	7.80
12.5	7.06
19.0	4.68
20.7	4.28
22.9	3.88
24.7	3.60

Ejemplo 199

Una mezcla de ácido (2E)-3-(1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-il)acrílico (220 mg), N,N'-carbonildiimidazol (137 mg) y N,N-dimetilformamida (6.0 ml) se agitó a temperatura ambiente

durante 1 hora, se añadieron pentan-1-sulfonamida (102 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (129 mg), y la mezcla se agitó a 100°C durante 4 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se vertió en ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:2, v/v) para dar (2E)-3-(1-{[3-cloro-5-(trifluorometil)piridin-2-il]metil}-3-isopropoxi-1H-pirazol-5-il)-N-(pentilsulfonil)acrilamida (30 mg, rendimiento: 10%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.89 (3 H, t, J = 7.2 Hz), 1.22 - 1.49 (10 H, m), 1.75 - 1.90 (2 H, m), 3.40 - 3.51 (2 H, m), 4.61 - 4.74 (1 H, m), 5.58 (2 H, s), 6.07 (1 H, s), 6.34 (1 H, d, J = 15.3 Hz), 7.62 (1 H, d, J = 15.3 Hz), 7.91 - 7.96 (1 H, m), 8.61 - 8.65 (1 H, m), 8.74 (1 H, m).

Ejemplo 200

Bajo enfriamiento con hielo, a una solución de ter-butil {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (9.03 g) en N,N-dimetilformamida (150 ml) se añadió hidruro de sodio (60% en aceite, 2.28 g), y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 30 min. La mezcla de reacción se enfrió en hielo otra vez, se añadió una solución de 1-(2,4-diclorobencil)-3-(metoximetoxi)-

1H-pirazol-5-carbaldehído (4.80 g) en N,N-dimetilformamida (40 ml), y la mezcla se agitó bajo una atmósfera de argón a 0°C durante 1 hora. La mezcla de reacción se vertió en una solución acuosa de cloruro de sodio saturado, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (1:9 - 2:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar ({(E)-2-[1-(2,4-diclorobencil)-3-(metoximetoxi)-1H-pirazol-5-il]vinil}sulfonil)carbamato de ter-butilo (3.16 g, rendimiento: 42%) en forma de cristales incoloros. Punto de fusión 139-140°C.

Ejemplo 201

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (1.00 g) en tetrahidrofurano (25 ml) se añadió N,N'-carbonildiimidazol (604 mg), y la mezcla se calentó a reflujo durante 1 h. Tras dejar enfriar hasta temperatura ambiente, se añadieron 3-metoxipropano-1-sulfonamida (0.57 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.70 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa

saturada de carbonato ácido de sodio y salmuera saturada, se secó (MgSO4), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 - 9:1, v/v) para dar una (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(3-metoxipropil)sulfonil]acrilamida (138 mg, rendimiento: 10%) como una forma amorfa blanca.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:2.01 - 2.16 (2 H, m), 3.30 (3 H, s), 3.44 (3 H, s), 3.47 (2 H, t, J = 5.9 Hz), 3.54 - 3.64 (2 H, m), 3.70 - 3.82 (2 H, m), 4.06 - 4.20 (2 H, m), 6.38 (1 H, d, J = 15.6 Hz), 6.68 - 6.76 (1 H, m), 6.91 (1 H, dd, J = 8.8, 2.5 Hz), 7.60 (1 H, d, J = 8.9 Hz), 7.79 (1 H, d, J = 15.6 Hz), 8.03 (1 H, d, J = 2.1 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 202

A una solución de ácido 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propanoico (0.50 g) en tetrahidrofurano (15 ml) se añadió N,N'-carbonildiimidazol (340 mg), y la mezcla se calentó a reflujo durante 1 h. Tras dejar enfriar hasta temperatura ambiente, se añadieron 3-metoxipropano-1-sulfonamida (0.31 g) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.40 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. La mezcla de reacción se concentró y el concentrado se disolvió en acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N,

una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-[(3-metoxipropil)sulfonil]propanamida (4.12 g, rendimiento: 99%) en forma de cristales blancos. Punto de fusión 114-115°C.

Ejemplo 203

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (499 mg) en diclorometano (5 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.30 ml) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se agregó 3-metil-1-butilamina (0.40 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1,

v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano luego de etanol-agua dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo {[(3-metilbutil)amino]sulfonil}carbamato de ter-butilo (85 mg, rendimiento: 12%) en forma de cristales blancos. Punto de fusión 123.0-123.5°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.0 Hz), 1.84 - 2.00 (2 H, m), 2.56 (2 H, t, J = 7.4 Hz), 3.15 - 3.27 (2 H, m), 3.44 (3 H, s), 3.53 (2 H, t, J = 5.2 Hz), 3.55 - 3.62 (1 H, m), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.09 (2 H, dd, J = 5.5, 4.0 Hz), 4.14 (2 H, t, J = 6.3 Hz), 5.40 (1 H, t, J = 5.8 Hz), 6.68 (1 H, d, J = 2.6 Hz), 6.83 (1 H, dd, J = 8.5, 2.6 Hz), 7.19 (1 H, d, J = 8.7 Hz), 7.47 (1 H, s), 8.01 (1 H, d, J = 2.1 Hz), 8.27 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 204

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (497 mg) en diclorometano (5 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-isopropoxietilamina (0.40 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de

reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (730 mg, rendimiento: 97%) en forma de cristales blancos. Punto de fusión 113.5-114.0°C.

La recristalización de los cristales crudos obtenidos en las mismas condiciones que en el Ejemplo 204 de etanol-hexano dio cristales. El patrón de difracción de polvos por rayos X de este cristal tal como se midió usando rayo de Cu-Kα (voltaje del tubo: 40 KV; corriente del tubo: 50 mA) como una fuente de radiación y RINT2100 tipo Ultima+ (Rigaku Corporation) se muestra en la Fig. 4.

Datos (pico principal) de la difracción de polvos por rayos X

Ángulo de difracción: 2θ (°)	Espaciado: valor d (angstrom)
7.74	11.4
11.0	8.01
15.5	5.70
18.7	4.75
20.8	4.27
23.9	3.72
27.5	3.24

1100

Ejemplo 205

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (495 mg) en N,N-dimetilformamida (5 ml) se añadió N,N'-carbonildiimidazol (296 mg), y la mezcla se agitó a 40°C durante 1 hora. Tras dejar enfriar hasta temperatura ambiente, se añadieron N-(4-metilciclohexil)sulfamida (254 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(4-metilciclohexil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (323 mg, rendimiento: 43%) en forma de cristales blancos. Punto de fusión 121.5-121.8°C.

Ejemplo 206

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

metoxietoxi)fenil]propan-1-ol (504 mg) en diclorometano (5 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-feniletilamina (0.40 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(2-feniletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (596 mg, rendimiento: 76%) en forma de cristales blancos. Punto de fusión 110-113°C.

Ejemplo 207

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (493 mg) en N,N-dimetilformamida (5 ml) se añadió N,N'-carbonildiimidazol (291 mg), y la mezcla se agitó a 40°C durante 1 hora. Tras dejar enfriar hasta temperatura ambiente, se añadieron N-[2-(2-

tienil)etil]sulfamida (275 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante la noche. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido de color amarillo pálido. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio ({[2-(2-tienil)etil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (319 mg, rendimiento: 41%) en forma de cristales blancos. Punto de fusión 117.5-118.0°C.

Ejemplo 208

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol (483 mg) en diclorometano (5 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se añadió 2-piridin-2-iletilamina (0.40 g), y la mezcla se agitó durante la noche a temperatura ambiente. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con

acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 9:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio {[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo (439 mg, rendimiento: 58%) en forma de un polvo blanco. Punto de fusión 91-93°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.78 - 1.97 (2 H, m), 2.53 (2 H, t, J = 7.4 Hz), 3.06 (2 H, t, J = 6.2 Hz), 3.43 (3 H, s), 3.52 (2 H, t, J = 6.2 Hz), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 3.98 - 4.15 (4 H, m), 6.37 (1 H, br. s.), 6.67 (1 H, d, J = 2.4 Hz), 6.81 (1 H, dd, J = 8.5, 2.6 Hz), 7.09 - 7.21 (3 H, m), 7.61 (1 H, ddd, J = 7.6, 7.6, 1.9 Hz), 7.99 (1 H, d, J = 1.9 Hz), 8.26 (1 H, dd, J = 2.1, 0.9 Hz), 8.49 (1 H, dd, J = 5.1, 1.9 Hz).

La recristalización de los cristales crudos obtenidos en las mismas condiciones que en el Ejemplo 208 de acetato de etilo-hexano dio cristales. El patrón de difracción de polvos por rayos X de este cristal tal como se midió usando rayo de Cu-Kα (voltaje del tubo: 40 KV; corriente del tubo: 50 mA) como una fuente de radiación y RINT2100 tipo Ultima+

(Rigaku Corporation) se muestra en la Fig. 5.

Datos (pico principal) de la difracción de polvos por rayos X

Ángulo de difracción: 2θ (°)	Espaciado: valor d (angstrom)
9.44	9.36
12.7	6.94
14.4	6.13
15.9	5.56
17.3	5.12
20.1	4.42
20.7	4.30
22.7	3.91
23.7	3.75

Ejemplo 209

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilpropanoico (495 mg) en diclorometano (10 ml) se añadieron 1-etil-3-(3-dimetilaminopropil)carbodiimida (242 mg), 4-dimetilaminopiridina (252 mg) y pentan-1-sulfonamida (243 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se

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sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metil-N-(pentilsulfonil)propanamida en forma de cristales blancos. Punto de fusión 136.5-138.0°C.

Ejemplo 210

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metoxipropanoico (512 mg) en diclorometano (10 ml) se añadieron 1-etil-3-(3-dimetilaminopropil)carbodiimida (269 mg), 4-dimetilaminopiridina (278 mg) y pentan-1-sulfonamida (266 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 65:35, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Los cristales obtenidos se sometieron a cromatografía en columna de gel de sílice, y se eluyeron con acetato de etilo-hexano (1:9 - 1:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-

hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metoxi-N-(pentilsulfonil)propanamida (154 mg, rendimiento: 23%) en forma de cristales blancos. Punto de fusión 76.0-78.0°C.

Ejemplo 211

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (220 mg) en diclorometano (10 ml) se añadieron 1-etil-3-(3-dimetilaminopropil)carbodiimida (201 mg), 4-dimetilaminopiridina (299 mg) y pentan-1-sulfonamida (106 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metil-N-(pentilsulfonil)acrilamida (158 mg, rendimiento: 55%) en forma de cristales blancos. Punto de fusión 108-111°C.

Ejemplo 212

A una solución de N-(aminosulfonil)-3-[2-{[3-cloro-

5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanamida (201 mg) en tetrahidrofurano (20 ml) se añadieron trifenilfosfina (143 mg), 1-butanol (0.10 ml) y una solución toluénica al 40% de azodicarboxilato de dietilo (0.30 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v) para dar un sólido blanco. Esto se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (hexano solo hasta acetato de etilo solo) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio N-(aminosulfonil)-N-butil-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanamida (30 mg, rendimiento: 13%) en forma de cristales blancos. Punto de fusión 102-103°C.

Ejemplo 213

A una solución de N-(aminosulfonil)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanamida (201 mg) en tetrahidrofurano (20 ml) se añadieron trifenilfosfina (143 mg), 2-metoxietanol (0.10 ml) y una solución toluénica al 40% de azodicarboxilato de dietilo (0.30 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de

reacción se concentró, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice y se eluyó con acetato de etilo-hexano (1:19 - 65:35, v/v) para dar un sólido blanco. Esto se sometió a cromatografía en columna con gel de sílice básica, y se eluyó con acetato de etilo-hexano (1:19 acetato de etilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio N-(aminosulfonil)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(2-metoxietil)propanamida (65 mg, rendimiento: 29%) en forma de cristales blancos. Punto de fusión 101.0-101.1°C.

Ejemplo 214

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propanoico (507 mg) en acetonitrilo (6 ml) se añadieron 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.25 g), 4-dimetilaminopiridina (335 mg) y N-pentilsulfamida (202 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo

hasta 9:1, v/v) para dar un sólido blanco. El sólido obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:4, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(pentilamino)sulfonil]propanamida (14 mg, rendimiento: 2%) en forma de cristales blancos. Punto de fusión 153.0-153.5°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.85 - 0.93 (3 H, m), 1.20 - 1.37 (4 H, m), 1.47 (2 H, tt, J = 7.3, 7.2 Hz), 2.57 (2 H, t, J = 7.2 Hz), 2.71 (2 H, q, J = 6.8 Hz), 2.92 (2 H, t, J = 7.3 Hz), 3.42 (3 H, s), 3.68 - 3.74 (2 H, m), 4.03 - 4.08 (2 H, m), 4.99 (1 H, t, J = 6.3 Hz), 6.55 (1 H, d, J = 2.4 Hz), 6.78 (1 H, dd, J = 8.5, 2.4 Hz), 7.19 (1 H, d, J = 8.5 Hz), 8.07 (1 H, d, J = 2.3 Hz), 8.35 (1 H, dd, J = 2.0, 0.8 Hz), 8.76 (1 H, s).

Ejemplo 215

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (837 mg) en acetonitrilo (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (515 mg), 4-dimetilaminopiridina (385 mg) y N-pentilsulfamida (336 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la

mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 7:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Los cristales se recristalizaron en etanol-agua para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(pentilamino)sulfonil]acrilamida (104 mg, rendimiento: 9%) en forma de cristales blancos. Punto de fusión 120-122°C.

Ejemplo 216

A una solución de ácido (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (300 mg) en diclorometano (10 ml) se añadieron 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.20 g), 4-dimetilaminopiridina (236 mg) y pentan-1-sulfonamida (115 mg), y la mezcla se agitó bajo enfriamiento con hielo durante 1 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55,

v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (139 mg, rendimiento: 35%) en forma de cristales blancos. Punto de fusión 104-106°C.

Ejemplo 217

A una solución de ácido (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrílico (789 mg) en acetonitrilo (6 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (356 mg), 4-dimetilaminopiridina (209 mg) y pentan-1-sulfonamida (176 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar una (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)-N-(pentilsulfonil)acrilamida (515 mg, rendimiento: 54%) en forma de un sólido incoloro. La recristalización en acetato de etilo-hexano dio un cristal blanco como dihidrato. Punto de fusión 108.0-108.5°C.

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Ejemplo 218

A una solución de (2E)-3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)-N-(pentilsulfonil)acrilamida (490 mg) en tetrahidrofurano (6 ml) se añadió una solución en tetrahidrofurano 1.0 M de fluoruro de tetra-n-butilamonio (1.20 ml), y la mezcla se agitó a 50°C durante 20 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (15:85 acetato de etilo solo, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxietoxi)fenil]-N-(pentilsulfonil)acrilamida monohidratada (234 mg, rendimiento: 69%) en forma de cristales blancos. Punto de fusión 112.5-112.8°C.

Ejemplo 219

A una solución de (2E)-3-[2-(4-aminofenoxi)-4-(2-metoxietoxi)fenil]acrilato de etilo (0.92 g) en acetonitrilo (10 ml) se añadieron cloruro cúprico (513 mg) y nitrito de t-butilo (0.45 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió agua

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a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua amoniacal al 28% p/p, agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v). El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 2:3, v/v) para dar un aceite anaranjado.

A una solución del aceite obtenido en tetrahidrofurano (1 ml) y etanol (1 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (2.5 ml), y la mezcla se agitó a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (2.5 ml) se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró.

A una solución del residuo obtenido en acetonitrilo (2 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (339 mg), 4-dimetilaminopiridina (208 mg) y pentan-1-sulfonamida (142 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada

de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 1:1, v/v) para dar un aceite incoloro. El residuo obtenido se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar hemihidrato de 3-[2-(4-clorofenoxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)propanamida (30 mg, rendimiento: 2%) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$)δ: 0.83 - 0.92 (3 H, m), 1.21 - 1.41 (4 H, m), 1.65 - 1.78 (2 H, m), 2.61 (2 H, t, J = 7.4 Hz), 2.91 (2 H, t, J = 7.4 Hz), 3.26 - 3.37 (2 H, m), 3.41 (3 H, s), 3.69 (2 H, dd, J = 5.5, 3.8 Hz), 4.01 (2 H, dd, J = 5.6, 3.9 Hz), 6.43 (1 H, d, J = 2.4 Hz), 6.61 - 6.72 (1 H, m), 6.86 - 6.93 (2 H, m), 7.16 (1 H, d, J = 8.5 Hz), 7.26 - 7.32 (2 H, m).

Luego se obtuvo un sólido de color amarillo pálido. La recristalización en acetato de etilo-éter diisopropílico dio una 3-[4-(2-metoxietoxi)-2-fenoxifenil]-N-(pentilsulfonil)propanamida (44 mg, rendimiento: 4%) en forma de cristales blancos. Punto de fusión 70.4-70.5°C.

Ejemplo 220

A una solución de ácido (2E)-3-(2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (409 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (311 mg), 4-dimetilaminopiridina (198 mg) y N-(2-feniletil)sulfamida (195 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-{[(2-feniletil)amino]sulfonil}acrilamida (246 mg, rendimiento: 42%) en forma de cristales blancos. Punto de fusión 147.0-147.5°C.

Ejemplo 221

A una solución de ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (216 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (154 mg), 4-dimetilaminopiridina (102 mg) y N-(3-metoxipropil)sulfamida (102 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró

para dar un sólido blanco. La recristalización en etanol-hexano dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-{[(3-metoxipropil)amino]sulfonil}-2-metilacrilamida (79 mg, rendimiento: 27%) en forma de cristales blancos. Punto de fusión 120.0-121.0°C.

Ejemplo 222

A una solución de ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (215 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (155 mg), 4-dimetilaminopiridina (108 mg) y N-(2-isopropoxietil)sulfamida (106 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-hexano dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-{[(2-isopropoxietil)amino]sulfonil}-2-metilacrilamida (160 mg, rendimiento: 54%) en forma de cristales blancos. Punto de fusión 137.5-137.7°C.

Ejemplo 223

A una solución de ácido (2E)-3-(2-{[3-cloro-5-

(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (210 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (170 mg), 4-dimetilaminopiridina (110 mg) y N-(4-metilciclohexil)sulfamida (88 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-{[(4-metilciclohexil)amino]sulfonil}acrilamida (130 mg, rendimiento: 49%) en forma de cristales blancos. Punto de fusión 176.8-177.2°C.

Ejemplo 224

A una solución de ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (218 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (161 mg), 4-dimetilaminopiridina (107 mg) y N-pentilsulfamida (75 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera

saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-[(pentilamino)sulfonil]acrilamida (176 mg, rendimiento: 69%) en forma de cristales blancos. Punto de fusión 137.8-138.5°C.

Ejemplo 225

A una solución de ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (210 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (159 mg), 4-dimetilaminopiridina (112 mg) y N-[2-(2-tienil)etil]sulfamida (89 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-({[2-(2-tienil)etil]amino}sulfonil)acrilamida (181 mg, rendimiento: 69%) en forma de cristales blancos. Punto de fusión 130-131°C.

Ejemplo 226

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-

metilacrílico (220 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (172 mg), 4-dimetilaminopiridina (117 mg) y N-pentilsulfamida (74 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metil-N-[(pentilamino)sulfonil]acrilamida (167 mg, rendimiento: 65%) en forma de cristales blancos. Punto de fusión 152.5-153.0°C.

Ejemplo 227

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (218 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (163 mg), 4-dimetilaminopiridina (109 mg) y N-(3-metoxipropil)sulfamida (102 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua

dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-{[(3-metoxipropil)amino]sulfonil}-2-metilacrilamida (83 mg, rendimiento: 28%) en forma de cristales blancos. Punto de fusión 121-122°C.

Ejemplo 228

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (420 mg) en acetonitrilo (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (276 mg), 4-dimetilaminopiridina (167 mg) y N-(2-feniletil)sulfamida (188 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. La recristalización en etanol-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-{[(2-feniletil)amino]sulfonil}acrilamida (75 mg, rendimiento: 13%) en forma de cristales blancos. Punto de fusión 85.0-85.5°C.

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Ejemplo 229

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (419 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (304 mg), 4-dimetilaminopiridina (193 mg) y 4-clorobencensulfonamida (174 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-N-[(4-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilamida (386 mg, rendimiento: 72%) en forma de cristales blancos. Punto de fusión 182.0-182.5°C.

Ejemplo 230

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (270 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (181 mg), 4-dimetilaminopiridina (114 mg) y 4-clorobencensulfonamida (114 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1

N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-N-[(4-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrilamida (194 mg, rendimiento: 54%) en forma de cristales blancos. Punto de fusión 145.7-145.8°C.

Ejemplo 231

A una solución de ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (216 mg) en acetonitrilo (2.5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (163 mg), 4-dimetilaminopiridina (143 mg) y N-(tetrahidrofurano-2-ilmetil)sulfamida (106 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-hexano dio (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-{[(tetrahidrofurano-2-ilmetil)amino]sulfonil}acrilamida (119 mg, rendimiento: 39%) en forma de cristales blancos. Punto de fusión 125.3-126.5°C.

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Ejemplo 232

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (424 mg) en acetonitrilo (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (319 mg), 4-dimetilaminopiridina (218 mg) y 3-clorobencensulfonamida (191 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-N-[(3-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilamida (587 mg, rendimiento: 100%) en forma de cristales blancos. Punto de fusión 157.0-158.0°C.

Ejemplo 233

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (446 mg) en acetonitrilo (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (327 mg), 4-dimetilaminopiridina (192 mg) y 3-clorobencensulfonamida (179 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1

N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-N-[(3-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrilamida (250 mg, rendimiento: 44%) en forma de cristales blancos. Punto de fusión 89-92°C.

Ejemplo 234

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (845 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (635 mg), 4-dimetilaminopiridina (331 mg) y 4-(trifluorometil)bencensulfonamida (446 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-{[4-(trifluorometil)fenil]sulfonil}acrilamida (794 mg, rendimiento: 64%) en forma de cristales blancos. Punto de

fusión 186.3-186.5°C.

Ejemplo 235

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (834 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (516 mg), 4-dimetilaminopiridina (331 mg) y 2-clorobencensulfonamida (383 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-N-[(2-clorofenil)sulfonil]-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrilamida (822 mg, rendimiento: 70%) en forma de cristales blancos. Punto de fusión 168-169°C.

Ejemplo 236

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (833 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (529 mg), 4-dimetilaminopiridina (343 mg) y p-toluensulfonamida (372 mg),

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y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(4-metilfenil)sulfonil]acrilamida (831 mg, rendimiento: 73%) en forma de cristales blancos. Punto de fusión 102.5-106.5°C.

Ejemplo 237

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (843 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (629 mg), 4-dimetilaminopiridina (346 mg) y 4-fluorobencensulfonamida (350 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(4-fluorofenil)sulfonil]acrilamida (670

mg, rendimiento: 58%) en forma de cristales blancos. Punto de fusión 183.0-184.0°C.

Ejemplo 238

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (843 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (600 mg), 4-dimetilaminopiridina (352 mg) y bencensulfonamida (307 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(fenilsulfonil)acrilamida (774 mg, rendimiento: 71%) en forma de cristales blancos. Punto de fusión 135.5-136.0°C.

Ejemplo 239

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (206 mg) en acetonitrilo (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (276 mg), 4-dimetilaminopiridina (97 mg) y 2-piridinsulfonamida (71 mg), y

la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(piridin-2-ilsulfonil)acrilamida (36 mg, rendimiento: 13%) en forma de cristales de mica blancos. Punto de fusión 164.0-165.0°C.

Ejemplo 240

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (846 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (620 mg), 4-dimetilaminopiridina (339 mg) y 3-piridinsulfonamida (314 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(piridin-3-ilsulfonil)acrilamida (557 mg, rendimiento: 51%) en

forma de cristales blancos. Punto de fusión 165-167°C.

Ejemplo 241

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (851 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (573 mg), 4-dimetilaminopiridina (336 mg) y m-toluensulfonamida (375 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(3-metilfenil)sulfonil]acrilamida (737 mg, rendimiento: 63%) en forma de cristales blancos. Punto de fusión 147.0-147.5°C.

Ejemplo 242

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (837 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (625 mg), 4-dimetilaminopiridina (339 mg) y 3-cianobencensulfonamida (369 mg), y la mezcla se agitó durante la noche a temperatura

ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(3-cianofenil)sulfonil]acrilamida (931 mg, rendimiento: 80%) en forma de cristales blancos. Punto de fusión 195-197°C.

Ejemplo 243

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (837 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (632 mg), 4-dimetilaminopiridina (332 mg) y trifluorometansulfonamida (306 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(trifluorometil)sulfonil]acrilamida (428 mg, rendimiento: 39%) en forma de cristales blancos.

Punto de fusión 125.5-128.0°C.

Ejemplo 244

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (860 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (795 mg), 4-dimetilaminopiridina (316 mg) y 2.2,2-trifluoroetansulfonamida (320 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metil-N-{(2.2,2-trifluoroetil)sulfonil}acrilamida (905 mg, rendimiento: 80%) en forma de cristales blancos. Punto de fusión 159.0-159.5°C.

Ejemplo 245

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metilacrílico (871 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (814 mg), 4-dimetilaminopiridina (355 mg) y trifluorometansulfonamida (305 mg), y la mezcla se agitó

durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2-metil-N-[(trifluorometil)sulfonil]acrilamida (980 mg, rendimiento: 86%) en forma de cristales blancos. Punto de fusión 146.0-147.0°C.

Ejemplo 246

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (840 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (634 mg), 4-dimetilaminopiridina (370 mg) y 2.2,2-trifluoroetansulfonamida (324 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(2.2,2-trifluoroetil)sulfonil]acrilamida

(847 mg, rendimiento: 76%) en forma de cristales blancos. Punto de fusión 146.0-147.5°C.

Ejemplo 247

A una solución de ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metilsulfonil)propoxi]fenil}acrílico (474 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (373 mg), 4-dimetilaminopiridina (186 mg) y pentan-1-sulfonamida (144 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y el sólido resultante se recogió por filtración y se lavó con agua para dar un sólido blanco. La recristalización en etanol-agua dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metilsulfonil)propoxi]fenil}-N-(pentilsulfonil)acrilamida (326 mg, rendimiento: 56%) en forma de cristales blancos. Punto de fusión 194-196°C.

Ejemplo 248

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-3-metilbutoxi)fenil]acrílico (446 mg) en acetonitrilo (5 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (360 mg), 4-dimetilaminopiridina (230 mg) y pentan-1-sulfonamida (150 mg), y la mezcla se agitó durante la noche a temperatura ambiente.

Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-hidroxi-3-metilbutoxi)fenil]-N-(pentilsulfonil)acrilamida (242 mg, rendimiento: 42%) en forma de cristales blancos. Punto de fusión 135.5-136.0°C.

Ejemplo 249

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metoximetoxi)-1.1-dimetilpropoxi]fenil}acrilato de etilo (975 mg) en tetrahidrofurano (2.5 ml) y etanol (2.5 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (5.0 ml), y la mezcla se agitó a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (5.0 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite de color amarillo pálido.

A una solución del aceite obtenido en acetonitrilo

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(10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (767 mg), 4-dimetilaminopiridina (293 mg) y pentan-1-sulfonamida (262 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v). El residuo obtenido se sometió a cromatografía líquida de alto rendimiento en fase inversa, y se eluyó con acetonitrilo-agua (2:3 a acetonitrilo solo, v/v) para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(metoximetoxi)-1.1-dimetilpropoxi]fenil}-N-(pentilsulfonil)acrilamida (222 mg, rendimiento: 21%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.73 - 0.97 (3 H, m), 1.18 - 1.36 (4 H, m), 1.38 (6 H, s), 1.65 - 1.89 (2 H, m), 2.03 (2 H, t, J = 7.1 Hz), 3.35 (3 H, s), 3.37 - 3.54 (2 H, m), 3.74 (2 H, t, J = 7.2 Hz), 4.61 (2 H, s), 6.45 (1 H, d, J = 15.6 Hz), 6.77 (1 H, d, J = 2.3 Hz), 6.93 (1 H, d, J = 8.3 Hz), 7.58 (1 H, d, J = 8.7 Hz), 7.80 (1 H, d, J = 15.6 Hz), 7.92 - 8.08 (1 H, m), 8.18 - 8.29 (1 H, m).

Ejemplo 250

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]acrílico (3.62 g) en acetonitrilo (40 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (3.21 g), 4-dimetilaminopiridina (1.54 g) y pentan-1-sulfonamida (1.27 g), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 1:1, v/v). El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 1:1, v/v). El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 9:1, v/v). El residuo se trituró con éter diisopropílico para dar un complejo de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]-N-(pentilsulfonil)acrilamida 0.10 éter diisopropílico-0.19 acetato de etilo (424 mg, rendimiento: 9%) en forma de un sólido blanco. La recristalización en acetona-hexano dio cristales blancos en forma de 0.23 solvato de

acetona. Punto de fusión 98-100°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.86 - 0.94 (3 H, m), 1.21 - 1.45 (4 H, m), 1.34 (6 H, s), 1.70 - 1.92 (2 H, m), 2.08 (1 H, s), 3.23 - 3.56 (2 H, m), 3.82 (2 H, s), 6.38 (1 H, d, J = 15.4 Hz), 6.71 (1 H, d, J = 2.5 Hz), 6.91 (1 H, dd, J = 8.8, 2.5 Hz), 7.61 (1 H, d, J = 8.8 Hz), 7.78 (1 H, d, J = 15.4 Hz), 8.03 (1 H, d, J = 2.2 Hz), 8.25 (1 H, dd, J = 2.2, 0.8 Hz).

Ejemplo 251

A una solución de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]acrílico (439 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (356 mg), 4-dimetilaminopiridina (206 mg) y pentan-1-sulfonamida (151 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-N-(pentilsulfonil)acrilamida

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(149 mg, rendimiento: 26%) en forma de cristales blancos. Punto de fusión 116.5-118.0°C.

Ejemplo 252

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetilpropanoico (1.21 g) en tetrahidrofurano (25 ml) se añadió N,N'-carbonildiimidazol (877 mg), y la mezcla se calentó a reflujo durante 1 h. Tras dejar enfriar hasta temperatura ambiente, se añadieron pentan-1-sulfonamida (817 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.80 ml) a la mezcla de reacción, y la mezcla se agitó durante 3 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (hexano solo hasta 2:3, v/v) para dar 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetil-N-(pentilsulfonil)propanamida (1.51 g, rendimiento: 96%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.82 - 0.95 (3 H, m), 1.25 (6 H, s), 1.28 - 1.48 (4 H, m), 1.75 (2 H, tt, J = 7.6, 7.6 Hz), 2.76 (2 H, s), 3.34 - 3.42 (2 H, m), 3.43 (3 H, s), 3.73 (2 H, dd, J = 5.4, 3.9 Hz), 4.09 (2 H, dd, J = 5.5, 4.0 Hz), 6.68 (1 H, d, J = 2.4 Hz), 6.82 (1 H, dd, J = 8.7, 2.6 Hz),

7.20 (1 H, d, J = 8.7 Hz), 7.82 (1 H, br. s.), 8.01 (1 H, d, J = 2.3 Hz), 8.28 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 253

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetil-N-(pentilsulfonil)propanamida (1.23 g) en metanol (2 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (2.12 ml) a temperatura ambiente, y la mezcla de reacción se concentró. El residuo obtenido se lavó con metanol frío para dar {3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-2.2-dimetilpropanoil}(pentilsulfonil)azanida de sodio (982 mg, rendimiento: 77%) en forma de cristales blancos. Punto de fusión 190.5-191.0°C.

Ejemplo 254

A una solución de ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}acrílico (2.45 g) en acetonitrilo (50 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (1.97 g), 4-dimetilaminopiridina (1.26 g) y pentan-1-sulfonamida (788 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó

($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}-N-(pentilsulfonil)acrilamida (1.70 g, rendimiento: 54%) en forma de cristales blancos. Punto de fusión 103.0-105.0°C.

Ejemplo 255

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}-N-(pentilsulfonil)acrilamida (569 mg) en tetrahidrofurano (10 ml) y metanol (10 ml) se añadió un complejo de paladio-carbón activado-etilenodiamina (61 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 12.5 h. La mezcla de reacción se filtró, y el filtrado se concentró. El residuo obtenido se disolvió en tetrahidrofurano (10 ml) y metanol (10 ml), se añadió un complejo de paladio-carbón activado-etilenodiamina (131 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró y el filtrado se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Los cristales obtenidos se sometieron a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 2:3, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-{2-{[3-

cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(2-metoxietoxi)propoxi]fenil}-N-(pentilsulfonil)propanamida (8 mg, rendimiento: 1%) en forma de cristales blancos. Punto de fusión 95.0-95.8°C.

Ejemplo 256

A una solución de ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metoxietoxi)etoxi]fenil}acrílico (1.86 g) en acetonitrilo (50 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (1.55 g), 4-dimetilaminopiridina (0.99 g) y pentan-1-sulfonamida (611 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metoxietoxi)etoxi]fenil}-N-(pentilsulfonil)acrilamida (1.01 g, rendimiento: 42%) en forma de cristales blancos. Punto de fusión 81.0-83.0°C.

Ejemplo 257

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metoxietoxi)etoxi]fenil}-N-(pentilsulfonil)acrilamida (280 mg)

en tetrahidrofurano (10 ml) y metanol (10 ml) se añadió un complejo de paladio-carbón activado-etilenodiamina (60 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 8 h. La mezcla de reacción se filtró y el filtrado se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio cristales blancos. Los cristales obtenidos se sometieron a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 3:2, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metoxietoxi)etoxi]fenil}-N-(pentilsulfonil)propanamida (26 mg, rendimiento: 9%) en forma de cristales blancos. Punto de fusión 76.0-77.5°C.

Ejemplo 258

A una solución de ácido 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propanoico (437 mg) en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (403 mg), 4-dimetilaminopiridina (179 mg) y pentan-1-sulfonamida (153 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó

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($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano, luego de etanol-agua dio 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-N-(pentilsulfonil)propanamida (351 mg, rendimiento: 62%) en forma de cristales blancos. Punto de fusión 115.0-115.2°C.

Ejemplo 259

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(ciclopropilmetoxi)propoxi]fenil}acrilato de etilo (0.66 g) en tetrahidrofurano (3 ml) y etanol (3 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4 ml), y la mezcla se agitó a 50°C durante 1 hora. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (4 ml) se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar una un aceite de color amarillo pálido.

A una solución del aceite obtenido en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (415 mg), 4-dimetilaminopiridina (269 mg) y pentan-1-sulfonamida (164 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se

lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 1:1, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[3-(ciclopropilmetoxi)propoxi]fenil}-N-(pentilsulfonil)acrilamida (301 mg, rendimiento: 46%) en forma de cristales blancos. Punto de fusión 124-125°C.

Ejemplo 260

A una solución de ácido (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)-3-metilfenil]acrílico (86 mg) en acetonitrilo (5 ml) se añadieron trietilamina (59 µl) y anhídrido 2-metil-6-nitrobenzoico (109 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Luego se añadieron 4-dimetilaminopiridina (51 mg) y pentan-1-sulfonamida (32 mg), y la mezcla se agitó durante la noche mientras se dejaba calentar hasta temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-[2-[(2,4-diclorobencil)oxi]-4-(2-metoxietoxi)-3-metilfenil]-N-(pentilsulfonil)acrilamida monohidratado (37 mg, rendimiento:

32%) en forma de cristales blancos. Punto de fusión 149-152°C.

En el Ejemplo 261-Ejemplo 423, para la HPLC preparativa en fase inversa, se utilizó un sistema UniPoint equipado con una columna YMC CombiPrep Pro C18, 50x20 mm, S-5 µm (Gilson) y las mezclas se eluyeron con acetonitrilo con contenido de 0.1% de ácido trifluoroacético-agua (5:95-100:0, v/v).

Ejemplo 261

Una solución de [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol (30 mg) en diclorometano (0.50 ml) se enfrió hasta 0°C, se añadió una solución de clorosulfonilisocianato (12.5 mg) en diclorometano (0.50 ml) y la mezcla se agitó durante 30 min. Una solución de piridina (19.0 mg) en diclorometano (0.50 ml) se añadió a la mezcla de reacción y la mezcla se siguió agitando a 0°C durante 30 min. Una solución de isopropilamina (14.2 mg) en diclorometano (0.50 ml) se añadió y la mezcla se siguió agitando durante la noche mientras se elevaba la temperatura hasta temperatura ambiente. La mezcla de reacción se extrajo con diclorometano (3.0 ml) y agua (2.0 ml), se fraccionó usando un tubo de PTFE (tubo de procesamiento de película de politetrafluoroetileno, fabricado por Whatman) y la capa de diclorometano se concentró. El residuo se disolvió en DMSO (0.50 ml) y se purificó por HPLC preparativa en fase inversa. Se añadió

solución acuosa al 5% de carbonato ácido de sodio (1.0 ml) a la fracción objeto y la mezcla se concentró. Se añadió agua (1.0 ml) al residuo, y la mezcla se extrajo con acetato de etilo (3.5 ml) y se fraccionó por deshidratante Presep™ (fabricado por Wako Pure Chemical Industries, Ltd.). La capa acuosa se extrajo con acetato de etilo (3.5 ml). Las capas de acetato de etilo se combinaron, y la mezcla se concentró con un aparato de soplado de nitrógeno para dar [(isopropilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo (25 mg, rendimiento: 57%). Pureza por LC-MS: 100%, m/z = 540[M-H$^+$], tiempo de retención = 1.89 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:1.06 (6 H, d, J = 6.4 Hz), 3.38 - 3.47 (1 H, m), 3.42 (3 H, s), 3.69 - 3.75 (2 H, m), 4.05 - 4.13 (2 H, m), 4.99 - 5.10 (3 H, m), 6.67 (1 H, d, J = 2.0 Hz), 6.82 (1 H, d, J = 6.6 Hz), 7.41 (1 H, d, J = 8.6 Hz), 7.97 (1 H, d, J = 1.7 Hz), 8.23 (1 H, s).

De la misma manera que en el Ejemplo 261, se hicieron reaccionar los alcoholes [2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]metanol, 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propan-1-ol, 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propan-1-ol, 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propan-1-ol y 3-[4-(2-metoxietoxi)-2-

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(tetrahidrofurano-2-ilmetoxi)fenil]propan-1-ol con varias aminas para dar los compuestos del Ejemplo 262-Ejemplo 423.

Ejemplo 262

{[(2-hidroxietil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 33%, pureza por LC-MS: 100%, m/z = 542[M-H$^+$], tiempo de retención = 1.68 min.

Ejemplo 263

{[(2-cianoetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 55%, pureza por LC-MS: 95%, m/z = 551[M-H$^+$], tiempo de retención = 1.73 min.

Ejemplo 264

[(ter-butilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 50%, pureza por LC-MS: 95%, m/z = 554[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 265

{[(3-hidroxipropil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 16%, pureza por LC-MS: 100%, m/z = 556[M-H$^+$], tiempo de retención = 1.71 min.

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Ejemplo 266

{[(2-metoxietil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 556[M-H$^+$], tiempo de retención = 1.77 min.

Ejemplo 267

[(ciclopentilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 30%, pureza por LC-MS: 95%, m/z = 566[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 268

{[(1-etilpropil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 55%, pureza por LC-MS: 100%, m/z = 568[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 269

{[(3-metilbutil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 52%, pureza por LC-MS: 100%, m/z = 568[M-H$^+$], tiempo de retención = 1.98 min.

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Ejemplo 270

{[(1.2-dimetilpropil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 56%, pureza por LC-MS: 100%, m/z = 568[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 271

{[(1-metilbutil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 568[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 272

{[(4-hidroxibutil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 22%, pureza por LC-MS: 100%, m/z = 570[M-H$^+$], tiempo de retención = 1.74 min.

Ejemplo 273

[(ciclohexilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 19%, pureza por LC-MS: 100%, m/z = 580[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 274

{[(tetrahidrofurano-2-

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ilmetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 54%, pureza por LC-MS: 100%, m/z = 582[M-H$^+$], tiempo de retención = 1.81 min.

Ejemplo 275

{[(1.3-dimetilbutil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 582[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 276

({[2-(acetilamino)etil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 23%, pureza por LC-MS: 100%, m/z = 583[M-H$^+$], tiempo de retención = 1.67 min.

Ejemplo 277

{[(2-isopropoxietil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 62%, pureza por LC-MS: 100%, m/z = 584[M-H$^+$], tiempo de retención = 1.88 min.

Ejemplo 278

({[1-(metoximetil)propil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

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metoxietoxi)bencilo

rendimiento: 59%, pureza por LC-MS: 93%, m/z = 584[M-H$^+$], tiempo de retención = 1.91 min.

Ejemplo 279

{[(3-etoxipropil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 584[M-H$^+$], tiempo de retención = 1.87 min.

Ejemplo 280

({[3-(metiltio)propil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 67%, pureza por LC-MS: 100%, m/z = 586[M-H$^+$], tiempo de retención = 1.88 min.

Ejemplo 281

[(bencilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 46%, pureza por LC-MS: 100%, m/z = 588[M-H$^+$], tiempo de retención = 1.91 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:3.39 (3 H, s), 3.64 - 3.74 (2 H, m), 3.93 - 4.03 (4 H, m), 4.89 (2 H, s), 5.49 (1 H, s), 6.59 (1 H, d, J = 1.7 Hz), 6.74 (1 H, s), 7.08 - 7.18 (5 H, m), 7.32 (1 H, d, J = 8.3 Hz), 7.88 (1 H, s), 8.16 (1 H, s).

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Ejemplo 282

{[(2-amino-2-oxoetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 10%, pureza por LC-MS: 100%, m/z = 555[M-H$^+$], tiempo de retención = 1.63 min.

Ejemplo 283

{[(ciclohexilmetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 594[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 284

[(cicloheptilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 37%, pureza por LC-MS: 100%, m/z = 594[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 285

{[(4-metilciclohexil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 44%, pureza por LC-MS: 100%, m/z = 594[M-H$^+$], tiempo de retención = 2.06 min.

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Ejemplo 286

{[(3-isopropoxipropil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 74%, pureza por LC-MS: 95%, m/z = 598[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 287

{[(2-feniletil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 61%, pureza por LC-MS: 100%, m/z = 602[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 288

({[2-(2-tienil)etil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 608[M-H$^+$], tiempo de retención = 2.03 min.

Ejemplo 289

{[(2-oxoazepan-3-il)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 51%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 1.80 min.

Ejemplo 290

[(2.3-dihidro-1H-inden-2-ilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 63%, pureza por LC-MS: 100%, m/z = 614[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 291

[(2.3-dihidro-1H-inden-1-ilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 55%, pureza por LC-MS: 100%, m/z = 614[M-H$^+$], tiempo de retención = 2.02 min.

Ejemplo 292

[(1.2,3.4-tetrahidronaftalen-1-ilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 56%, pureza por LC-MS: 100%, m/z = 628[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 293

{[(2-fenoxietil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 70%, pureza por LC-MS: 95%, m/z = 618[M-H$^+$], tiempo de retención = 1.94 min.

Ejemplo 294

{[(4-metoxibencil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 66%, pureza por LC-MS: 95%, m/z = 618[M-H$^+$], tiempo de retención = 1.92 min.

Ejemplo 295

({[3-(2-oxopirrolidin-1-il)propil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 41%, pureza por LC-MS: 100%, m/z = 623[M-H$^+$], tiempo de retención = 1.76 min.

Ejemplo 296

(pirrolidin-1-ilsulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 65%, pureza por LC-MS: 95%, m/z = 552[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 297

(piperidin-1-ilsulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 566[M-H$^+$], tiempo de retención = 1.99 min.

Ejemplo 298

{[(2-metoxietil)(metil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

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metoxietoxi)bencilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 570[M-H$^+$], tiempo de retención = 1.89 min.

Ejemplo 299

[(4-metilpiperidin-1-il)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 46%, pureza por LC-MS: 100%, m/z = 580[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 300

[(dipropilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 582[M-H$^+$], tiempo de retención = 2.15 min.

Ejemplo 301

{[etil(2-metoxietil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 62%, pureza por LC-MS: 100%, m/z = 584[M-H$^+$], tiempo de retención = 1.97 min.

Ejemplo 302

(tiomorfolin-4-ilsulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 49%, pureza por LC-MS: 97%, m/z = 584[M-H$^+$], tiempo de retención = 1.88 min.

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Ejemplo 303

{[ciclohexil(metil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 61%, pureza por LC-MS: 100%, m/z = 594[M-H$^+$], tiempo de retención = 2.15 min.

Ejemplo 304

{[(2R)-2-(metoximetil)pirrolidin-1-il]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 54%, pureza por LC-MS: 95%, m/z = 596[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 305

{[(2S)-2-(metoximetil)pirrolidin-1-il]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 61%, pureza por LC-MS: 95%, m/z = 596[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 306

{[(2R,6S)-2.6-dimetilmorfolin-4-il]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 51%, pureza por LC-MS: 95%, m/z = 596[M-H$^+$], tiempo de retención = 1.85 min.

Ejemplo 307

(1.3-dihidro-2H-isoindol-2-ilsulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 47%, pureza por LC-MS: 100%, m/z = 600[M-H$^+$], tiempo de retención = 1.97 min.

Ejemplo 308

{[bencil(metil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 51%, pureza por LC-MS: 100%, m/z = 602[M-H$^+$], tiempo de retención = 2.03 min.

Ejemplo 309

{[4-(aminocarbonil)piperidin-1-il]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 3%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 1.70 min.

Ejemplo 310

{[3-(aminocarbonil)piperidin-1-il]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 30%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 1.70 min.

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Ejemplo 311

{[3-(acetilamino)pirrolidin-1-il]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 37%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 1.70 min.

Ejemplo 312

({[2-(dimetilamino)etil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 33%, pureza por LC-MS: 100%, m/z = 569[M-H$^+$], tiempo de retención = 1.67 min.

Ejemplo 313

[(piperidin-1-ilamino)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 5%, pureza por LC-MS: 90%, m/z = 581[M-H$^+$], tiempo de retención = 1.65 min.

Ejemplo 314

({[3-(dimetilamino)propil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 53%, pureza por LC-MS: 100%, m/z = 583[M-H$^+$], tiempo de retención = 1.67 min.

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Ejemplo 315

{[(2-pirrolidin-1-iletil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 31%, pureza por LC-MS: 100%, m/z = 595[M-H$^+$], tiempo de retención = 1.70 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:1.89 - 2.00 (4 H, m), 3.07 (2 H, t, J = 7.0 Hz), 3.12 - 3.24 (4 H, m), 3.26 - 3.33 (2 H, t, J = 6.9 Hz), 3.44 (3 H, s), 3.72 - 3.75 (2 H, m), 4.09 - 4.12 (2 H, m), 4.92 (2 H, s), 6.68 (1 H, d, J = 2.5 Hz), 6.88 (1 H, dd, J = 8.6, 2.5 Hz), 7.48 (1 H, d, J = 8.6 Hz), 7.99 (1 H, d, J = 2.2 Hz), 8.22 (1 H, d, J = 1.2 Hz).

Ejemplo 316

{[(piridin-2-ilmetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 589[M-H$^+$], tiempo de retención = 1.77 min.

Ejemplo 317

{[(piridin-4-ilmetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 49%, pureza por LC-MS: 100%, m/z = 589[M-H$^+$], tiempo de retención = 1.72 min.

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Ejemplo 318

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 603[M-H$^+$], tiempo de retención = 1.80 min.

Ejemplo 319

{[(2-piridin-4-iletil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 67%, pureza por LC-MS: 100%, m/z = 603[M-H$^+$], tiempo de retención = 1.75 min.

Ejemplo 320

{[(2-piridin-3-iletil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 54%, pureza por LC-MS: 100%, m/z = 603[M-H$^+$], tiempo de retención = 1.77 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:2.61 (2 H, d, J = 3.7 Hz), 3.00 - 3.09 (2 H, m), 3.39 (3 H, s), 3.62 - 3.69 (2 H, m), 3.93 - 4.00 (2 H, m), 4.89 (2 H, s), 5.45 - 5.57 (1 H, m), 6.58 (1 H, d, J = 2.2 Hz), 6.69 (1 H, d, J = 8.8 Hz), 7.02 (1 H, m), 7.33 (2 H, d, J = 8.8 Hz), 7.87 (1 H, d, J = 2.2 Hz), 8.14 (1 H, d, J = 1.0 Hz), 8.25 - 8.34 (2 H, m).

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Ejemplo 321

({[3-(1H-imidazol-1-il)propil]amino}sulfonil)carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 41%, pureza por LC-MS: 100%, m/z = 606[M-H$^+$], tiempo de retención = 1.70 min.

Ejemplo 322

{[(2-morfolin-4-iletil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 611[M-H$^+$], tiempo de retención = 1.72 min.

Ejemplo 323

{[(2-anilinoetil)amino]sulfonil}carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 49%, pureza por LC-MS: 100%, m/z = 617[M-H$^+$], tiempo de retención = 1.91 min.

Ejemplo 324

[(4-metilpiperazin-1-il)sulfonil]carbamato de 2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)bencilo

rendimiento: 20%, pureza por LC-MS: 100%, m/z = 581[M-H$^+$], tiempo de retención = 1.67 min.

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Ejemplo 325

[(isopropilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 51%, pureza por LC-MS: 100%, m/z = 568[M-H$^+$], tiempo de retención = 1.96 min.

Ejemplo 326

{[(2-hidroxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 46%, pureza por LC-MS: 100%, m/z = 570[M-H$^+$], tiempo de retención = 1.76 min.

Ejemplo 327

{[(2-cianoetil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 64%, pureza por LC-MS: 95%, m/z = 579[M-H$^+$], tiempo de retención = 1.79 min.

Ejemplo 328

[(ter-butilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 52%, pureza por LC-MS: 100%, m/z = 582[M-H$^+$], tiempo de retención = 2.02 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:1.30 (9 H, s), 1.86 - 1.94

(2 H, m), 2.52 (2 H, t, J = 7.5 Hz), 3.43 (3 H, s), 3.69 - 3.75 (2 H, m), 4.05 - 4.13 (4 H, m), 5.08 (1 H, s), 6.67 (1 H, d, J = 2.5 Hz), 6.81 (1 H, dd, J = 8.3, 2.5 Hz), 7.17 (1 H, d, J = 8.6 Hz), 7.99 (1 H, d, J = 2.2 Hz), 8.26 (1 H, s).

Ejemplo 329

{[(3-hidroxipropil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 47%, pureza por LC-MS: 100%, m/z = 584[M-H$^+$], tiempo de retención = 1.78 min.

Ejemplo 330

{[(2-metoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 65%, pureza por LC-MS: 90%, m/z = 584[M-H$^+$], tiempo de retención = 1.85 min.

Ejemplo 331

[(ciclopentilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 594[M-H$^+$], tiempo de retención = 2.02 min.

Ejemplo 332

{[(1-etilpropil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-

metoxietoxi)fenil]propilo

rendimiento: 62%, pureza por LC-MS: 100%, m/z = 596[M-H$^+$], tiempo de retención = 2.08 min.

Ejemplo 333

{[(3-metilbutil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z = 596[M-H$^+$], tiempo de retención = 2.06 min.

Ejemplo 334

{[(1.2-dimetilpropil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 596[M-H$^+$], tiempo de retención = 2.07 min.

Ejemplo 335

{[(1-metilbutil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z = 596[M-H$^+$], tiempo de retención = 2.08 min.

Ejemplo 336

{[(4-hidroxibutil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

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rendimiento: 45%, pureza por LC-MS: 100%, m/z = 598[M-H$^+$], tiempo de retención = 1.80 min.

Ejemplo 337

[(ciclohexilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 60%, pureza por LC-MS: 100%, m/z = 608[M-H$^+$], tiempo de retención = 2.07 min.

Ejemplo 338

{[(tetrahidrofurano-2-ilmetil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 66%, pureza por LC-MS: 100%, m/z = 610[M-H$^+$], tiempo de retención = 1.88 min.

Ejemplo 339

{[(1.3-dimetilbutil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 610[M-H$^+$], tiempo de retención = 2.13 min.

Ejemplo 340

({[2-(acetilamino)etil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

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rendimiento: 25%, pureza por LC-MS: 100%, m/z = 611[M-H$^+$], tiempo de retención = 1.74 min.

Ejemplo 341

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 56%, pureza por LC-MS: 100%, m/z = 612[M-H$^+$], tiempo de retención = 1.94 min.

Ejemplo 342

({[1-(metoximetil)propil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 54%, pureza por LC-MS: 95%, m/z = 612[M-H$^+$], tiempo de retención = 1.98 min.

Ejemplo 343

{[(3-etoxipropil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 612[M-H$^+$], tiempo de retención = 1.94 min.

Ejemplo 344

({[3-(metiltio)propil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z =

^{1}H-RMN (400 MHz, $CDCl_3$)δ:1.34 - 1.60 (10 H, m), 1.87 - 1.96 (4 H, m), 2.53 (2 H, t, J = 7.3 Hz), 3.43 (3 H, s), 3.38 - 3.46 (1 H, m), 3.70 - 3.75 (2 H, m), 4.05 - 4.14 (4 H, m), 5.00 - 5.09 (1 H,m), 6.68 (1 H, d, J = 2.2 Hz), 6.82 (1 H, dd, J = 8.6, 2.5 Hz), 7.18 (1 H, d, J = 8.6 Hz), 8.00 (1 H, d, J = 2.0 Hz), 8.26 (1 H, s).

Ejemplo 349

[(cicloheptilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 58%, pureza por LC-MS: 100%, m/z = 622[M-H$^+$], tiempo de retención = 2.13 min.

Ejemplo 350

{[(3-isopropoxipropil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 53%, pureza por LC-MS: 100%, m/z = 626[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 351

{[(2-feniletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 54%, pureza por LC-MS: 100%, m/z = 630[M-H$^+$], tiempo de retención = 2.03 min.

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Ejemplo 352

({[2-(2-tienil)etil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 47%, pureza por LC-MS: 100%, m/z = 636[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 353

{[(2-oxoazepan-3-il)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 90%, m/z = 637[M-H$^+$], tiempo de retención = 1.81 min.

Ejemplo 354

[(2.3-dihidro-1H-inden-2-ilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 54%, pureza por LC-MS: 100%, m/z = 642[M-H$^+$], tiempo de retención = 2.04 min.

Ejemplo 355

[(2.3-dihidro-1H-inden-1-ilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 51%, pureza por LC-MS: 100%, m/z = 642[M-H$^+$], tiempo de retención = 2.08 min.

Ejemplo 356

[(1.2,3.4-tetrahidronaftalen-1-ilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 51%, pureza por LC-MS: 100%, m/z = 656[M-H$^+$], tiempo de retención = 2.11 min.

Ejemplo 357

{[(2-fenoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 47%, pureza por LC-MS: 100%, m/z = 646[M-H$^+$], tiempo de retención = 2.00 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:1.77 - 1.89 (2 H, m), 2.50 (2 H, t, J = 7.2 Hz), 3.42 (3 H, s), 3.38 - 3.47 (2 H, m), 3.65 - 3.73 (2 H, m), 3.98 - 4.08 (6 H, m), 5.53 - 5.65 (1 H, m), 6.66 (1 H, d, J = 2.5 Hz), 6.76 - 6.86 (3 H, m), 6.92 (1 H, t, J = 7.1 Hz), 7.13 (1 H, d, J = 8.6 Hz), 7.23 (2 H, t, J = 7.8 Hz), 7.98 (1 H, d, J = 2.0 Hz), 8.25 (1 H, s).

Ejemplo 358

{[(4-metoxibencil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 100%, m/z = 646[M-H$^+$], tiempo de retención = 1.98 min.

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Ejemplo 359

({[3-(2-oxopirrolidin-1-il)propil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 40%, pureza por LC-MS: 82%, m/z = 651[M-H$^+$], tiempo de retención = 1.80 min.

Ejemplo 360

(pirrolidin-1-ilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 580[M-H$^+$], tiempo de retención = 2.00 min.

Ejemplo 361

(piperidin-1-ilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z = 594[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 362

{[(2-metoxietil)(metil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z = 598[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 363

[(4-metilpiperidin-1-il)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 46%, pureza por LC-MS: 94%, m/z = 608[M-H$^+$], tiempo de retención = 2.11 min.

Ejemplo 364

[(dipropilamino)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 610[M-H$^+$], tiempo de retención = 2.19 min.

Ejemplo 365

{[etil(2-metoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 612[M-H$^+$], tiempo de retención = 2.02 min.

Ejemplo 366

(tiomorfolin-4-ilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z = 612[M-H$^+$], tiempo de retención = 1.94 min.

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Ejemplo 367

{[ciclohexil(metil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 60%, pureza por LC-MS: 100%, m/z = 622[M-H$^+$], tiempo de retención = 2.19 min.

Ejemplo 368

{[(2R)-2-(metoximetil)pirrolidin-1-il]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 52%, pureza por LC-MS: 100%, m/z = 624[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 369

{[(2S)-2-(metoximetil)pirrolidin-1-il]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 59%, pureza por LC-MS: 100%, m/z = 624[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 370

{[(2R,6S)-2.6-dimetilmorfolin-4-il]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 55%, pureza por LC-MS: 100%, m/z = 624[M-H$^+$], tiempo de retención = 1.92 min.

Ejemplo 371

(1.3-dihidro-2H-isoindol-2-ilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 56%, pureza por LC-MS: 100%, m/z = 628[M-H$^+$], tiempo de retención = 2.04 min.

Ejemplo 372

{[bencil(metil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 57%, pureza por LC-MS: 100%, m/z = 630[M-H$^+$], tiempo de retención = 2.10 min.

Ejemplo 373

{[4-(aminocarbonil)piperidin-1-il]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 6%, pureza por LC-MS: 100%, m/z = 637[M-H$^+$], tiempo de retención = 1.76 min.

Ejemplo 374

{[3-(aminocarbonil)piperidin-1-il]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 47%, pureza por LC-MS: 100%, m/z =

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637[M-H$^+$], tiempo de retención = 1.77 min.

Ejemplo 375

{[3-(acetilamino)pirrolidin-1-il]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 100%, m/z = 637[M-H$^+$], tiempo de retención = 1.77 min.

Ejemplo 376

({[2-(dimetilamino)etil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 49%, pureza por LC-MS: 100%, m/z = 597[M-H$^+$], tiempo de retención = 1.72 min.

Ejemplo 377

({[3-(dimetilamino)propil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 39%, pureza por LC-MS: 100%, m/z = 611[M-H$^+$], tiempo de retención = 1.72 min.

Ejemplo 378

{[(2-pirrolidin-1-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 100%, m/z = 623[M-H$^+$], tiempo de retención = 1.74 min.

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Ejemplo 379

{[(piridin-2-ilmetil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 43%, pureza por LC-MS: 100%, m/z = 617[M-H$^+$], tiempo de retención = 1.83 min.

Ejemplo 380

{[(piridin-4-ilmetil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 100%, m/z = 617[M-H$^+$], tiempo de retención = 1.78 min.

Ejemplo 381

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 49%, pureza por LC-MS: 100%, m/z = 631[M-H$^+$], tiempo de retención = 1.87 min.

Ejemplo 382

{[(2-piridin-4-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 100%, m/z = 631[M-H$^+$], tiempo de retención = 1.81 min.

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Ejemplo 383

{[(2-piridin-3-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 43%, pureza por LC-MS: 100%, m/z = 631[M-H$^+$], tiempo de retención = 1.83 min.

Ejemplo 384

({[3-(1H-imidazol-1-il)propil]amino}sulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 39%, pureza por LC-MS: 100%, m/z = 634[M-H$^+$], tiempo de retención = 1.76 min.

Ejemplo 385

{[(2-morfolin-4-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 46%, pureza por LC-MS: 100%, m/z = 639[M-H$^+$], tiempo de retención = 1.77 min.

Ejemplo 386

{[(2-anilinoetil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 47%, pureza por LC-MS: 89%, m/z = 645[M-H$^+$], tiempo de retención = 1.97 min.

Ejemplo 387

[(4-metilpiperazin-1-il)sulfonil]carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo

rendimiento: 36%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 1.72 min.

Ejemplo 388

[(pentilamino)sulfonil]carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 21%, pureza por LC-MS: 100%, m/z = 499[M-H$^+$], tiempo de retención = 2.11 min.

Ejemplo 389

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 13%, pureza por LC-MS: 100%, m/z = 515[M-H$^+$], tiempo de retención = 2.06 min.

Ejemplo 390

{[(2-feniletil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 16%, pureza por LC-MS: 100%, m/z = 533[M-H$^+$], tiempo de retención = 2.14 min.

Ejemplo 391

({[2-(2-tienil)etil]amino}sulfonil)carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 12%, pureza por LC-MS: 100%, m/z =

539[M-H$^+$], tiempo de retención = 2.13 min.

Ejemplo 392

{[(2-fenoxietil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 19%, pureza por LC-MS: 87%, m/z = 549[M-H$^+$], tiempo de retención = 2.09 min.

Ejemplo 393

({[2-(2-metoxifenil)etil]amino}sulfonil)carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 18%, pureza por LC-MS: 100%, m/z = 563[M-H$^+$], tiempo de retención = 2.10 min.

Ejemplo 394

{[(2.2-difeniletil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 23%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 2.26 min.

Ejemplo 395

{[(1.2-difeniletil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 30%, pureza por LC-MS: 100%, m/z = 609[M-H$^+$], tiempo de retención = 2.23 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:1.30 - 1.42 (2 H, m), 1.45 - 1.68 (4 H, m), 1.69 - 1.79 (4 H, m), 1.88 - 1.97 (2 H, m), 2.45 - 2.52 (2 H, m), 3.01 - 3.09 (1 H, m), 3.12 - 3.18 (1 H, m), 3.44 (3 H, s), 3.71 - 3.76 (2 H, m), 3.79 - 3.84 (1 H, m),

3.86 - 3.91 (1 H, m), 4.05 - 4.11 (2 H, m), 4.18 - 4.25 (1 H, m), 4.59 - 4.67 (1 H, m), 5.59 - 5.67 (1 H, m), 6.34 - 6.40 (1 H, m), 6.50 (3 H, d, J = 2.2 Hz), 6.92 (1 H, d, J = 8.3 Hz), 6.97 - 7.08 (3 H, m), 7.14 - 7.24 (7 H, m).

Ejemplo 396

{[(piridin-2-ilmetil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 23%, pureza por LC-MS: 81%, m/z = 520[M-H$^+$], tiempo de retención = 2.03 min.

Ejemplo 397

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 27%, pureza por LC-MS: 100%, m/z = 534[M-H$^+$], tiempo de retención = 2.04 min.

Ejemplo 398

({[(5-metilpirazin-2-il)metil]amino}sulfonil)carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 28%, pureza por LC-MS: 100%, m/z = 535[M-H$^+$], tiempo de retención = 1.99 min.

Ejemplo 399

{[(3-metoxipropil)amino]sulfonil}carbamato de 3-[2-(ciclohexiloxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 20%, pureza por LC-MS: 100%, m/z = 501[M-H$^+$], tiempo de retención = 2.08 min.

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Ejemplo 400

[(pentilamino)sulfonil]carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 57%, pureza por LC-MS: 88%, m/z = 471[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 401

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 37%, pureza por LC-MS: 100%, m/z = 487[M-H$^+$], tiempo de retención = 2.04 min.

Ejemplo 402

{[(2-feniletil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 36%, pureza por LC-MS: 100%, m/z = 505[M-H$^+$], tiempo de retención = 2.05 min.

Ejemplo 403

({[2-(2-tienil)etil]amino}sulfonil)carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 50%, pureza por LC-MS: 100%, m/z = 511[M-H$^+$], tiempo de retención = 2.07 min.

Ejemplo 404

{[(2-fenoxietil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 48%, pureza por LC-MS: 89%, m/z = 521[M-H$^+$], tiempo de retención = 2.04 min.

Ejemplo 405

({[2-(2-metoxifenil)etil]amino}sulfonil)carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 46%, pureza por LC-MS: 100%, m/z = 535[M-H$^+$], tiempo de retención = 2.06 min.

Ejemplo 406

{[(2.2-difeniletil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 70%, pureza por LC-MS: 100%, m/z = 581[M-H$^+$], tiempo de retención = 2.12 min.

^{1}H-RMN (400 MHz, $CDCl_3$)δ:0.23 - 0.31 (2 H, m), 0.49 - 0.58 (2 H, m), 1.17 - 1.28 (1 H, m), 1.78 - 1.90 (2 H, m), 2.59 (2 H, t, J = 7.3 Hz), 3.43 (3 H, s), 3.63 (2 H, d, J = 7.8 Hz), 3.69 - 3.76 (4 H, m), 3.97 - 4.07 (4 H, m), 4.20 (1 H, t, J = 7.8 Hz), 5.03 (1 H, s), 6.36 (1 H, d, J = 8.3 Hz), 6.44 (1 H, d, J = 1.7 Hz), 6.94 (1 H, d, J = 8.1 Hz), 7.11 - 7.25 (1 H, m).

Ejemplo 407

{[(1.2-difeniletil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 44%, pureza por LC-MS: 100%, m/z = 581[M-H$^+$], tiempo de retención = 2.12 min.

Ejemplo 408

{[(piridin-2-ilmetil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

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rendimiento: 37%, pureza por LC-MS: 100%, m/z = 492[M-H$^+$], tiempo de retención = 1.97 min.

Ejemplo 409

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 52%, pureza por LC-MS: 100%, m/z = 506[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 410

({[(5-metilpirazin-2-il)metil]amino}sulfonil)carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 68%, pureza por LC-MS: 100%, m/z = 507[M-H$^+$], tiempo de retención = 1.93 min.

Ejemplo 411

{[(3-metoxipropil)amino]sulfonil}carbamato de 3-[2-(ciclopropilmetoxi)-4-(2-metoxietoxi)fenil]propilo

rendimiento: 43%, pureza por LC-MS: 100%, m/z = 473[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 412

[(pentilamino)sulfonil]carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 51%, pureza por LC-MS: 81%, m/z = 501[M-H$^+$], tiempo de retención = 2.08 min.

Ejemplo 413

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-

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[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 36%, pureza por LC-MS: 100%, m/z = 517[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 414

{[(2-feniletil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 45%, pureza por LC-MS: 100%, m/z = 535[M-H$^+$], tiempo de retención = 2.01 min.

Ejemplo 415

({[2-(2-tienil)etil]amino}sulfonil)carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 46%, pureza por LC-MS: 100%, m/z = 541[M-H$^+$], tiempo de retención = 1.99 min.

Ejemplo 416

{[(2-fenoxietil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 54%, pureza por LC-MS: 89%, m/z = 551[M-H$^+$], tiempo de retención = 2.02 min.

Ejemplo 417

({[2-(2-metoxifenil)etil]amino}sulfonil)carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 49%, pureza por LC-MS: 100%, m/z =

565[M-H$^+$], tiempo de retención = 2.03 min.

Ejemplo 418

{[(2.2-difeniletil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 41%, pureza por LC-MS: 100%, m/z = 611[M-H$^+$], tiempo de retención = 2.07 min.

Ejemplo 419

{[(1.2-difeniletil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 41%, pureza por LC-MS: 100%, m/z = 611[M-H$^+$], tiempo de retención = 2.09 min.

Ejemplo 420

{[(piridin-2-ilmetil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 17%, pureza por LC-MS: 88%, m/z = 522[M-H$^+$], tiempo de retención = 1.96 min.

Ejemplo 421

{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 17%, pureza por LC-MS: 100%, m/z = 536[M-H$^+$], tiempo de retención = 1.98 min.

Ejemplo 422

({[(5-metilpirazin-2-

il)metil]amino}sulfonil)carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 18%, pureza por LC-MS: 100%, m/z = 537[M-H$^+$], tiempo de retención = 1.86 min.

Ejemplo 423

{[(3-metoxipropil)amino]sulfonil}carbamato de 3-[4-(2-metoxietoxi)-2-(tetrahidrofurano-2-ilmetoxi)fenil]propilo

rendimiento: 21%, pureza por LC-MS: 100%, m/z = 503[M-H$^+$], tiempo de retención = 1.95 min.

Ejemplo 424

A una solución de ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}acrílico (1.73 g) en acetonitrilo (30 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (1.49 g), 4-dimetilaminopiridina (0.95 g) y pentan-1-sulfonamida (592 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:19 - 45:55, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-

il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}-N-(pentilsulfonil)acrilamida (952 mg, rendimiento: 42%) en forma de cristales blancos. Punto de fusión 104.6-106.5°C.

Ejemplo 425

A una solución de 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}propanoato de etilo (0.77 g) en tetrahidrofurano (4 ml) y etanol (4 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4 ml), y la mezcla se agitó a 50°C durante 30 min. Tras dejar enfriar hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (4 ml) se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró para dar un aceite amarillo.

A una solución del aceite obtenido en acetonitrilo (10 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (588 mg), 4-dimetilaminopiridina (283 mg) y pentan-1-sulfonamida (233 mg), y la mezcla se agitó durante la noche a temperatura ambiente. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de cloruro de amonio, y salmuera saturada, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se

sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:9 - 55:45, v/v) para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}-N-(pentilsulfonil)propanamida (361 mg, rendimiento: 40%) en forma de cristales blancos. Punto de fusión 96.5-97.5°C.

Ejemplo 426

A una solución de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propan-1-ol (274 mg) en tolueno (8 ml) bajo enfriamiento con hielo se añadió clorosulfonilisocianato (109 mg), y la mezcla se agitó durante 30 min. Se agregó piridina (175 mg) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se adicionó una solución al 28% de amoníaco (268 mg), y la mezcla se agitó a temperatura ambiente durante 1.5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio (aminosulfonil)carbamato de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propilo (210 mg, rendimiento: 58%) en forma de cristales incoloros. Punto de fusión 153.2-153.8°C.

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Ejemplo 427

A una solución de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propan-1-ol (404 mg) en tolueno (10 ml) se añadió clorosulfonilisocianato (161 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (258 mg) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se agregó 2-(2-aminoetil)-piridina (796 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1 - 7:3, v/v) para dar un {[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propilo (328 g, rendimiento: 50%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.82 - 1.95 (2 H, m), 2.54 (2 H, t, J = 7.4 Hz), 3.06 (2 H, t, J = 6.3 Hz), 3.43 (3 H, s), 3.48 - 3.54 (2 H, m), 3.72 (2 H, dd, J = 5.5, 4.0 Hz), 4.03 - 4.14 (4 H, m), 6.60 - 6.66 (1 H, m), 6.76 (1 H, dd, J = 8.5, 2.6 Hz), 7.10 - 7.19 (3 H, m), 7.57 - 7.65 (1 H, m), 7.76 - 7.80 (1 H, m), 7.95 (1 H, d, J = 2.4 Hz), 8.47 - 8.52 (1 H, m).

Ejemplo 428

A una solución de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propan-1-ol (406 mg) en tolueno (10 ml) se añadió clorosulfonilisocianato (162 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (259 mg) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se añadió 3-metoxipropilamina (584 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3 - 3:2, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(3-metoxipropil)amino]sulfonil}carbamato de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propilo (435 mg, rendimiento: 70%) en forma de cristales incoloros. Punto de fusión 87.9-89.0°C.

Ejemplo 429

A una solución de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propan-1-ol (400 mg) en tolueno (10 ml) se añadió clorosulfonilisocianato (160 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (255 mg) a la mezcla de reacción y la

mezcla se agitó durante 1 hora. Se agregó éter 2-aminoetilisopropílico (665 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 1:1, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-[(3,5-dicloropiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]propilo (256 mg, rendimiento: 41%) en forma de cristales incoloros. Punto de fusión 87.5-88.4°C.

Ejemplo 430

A una solución de 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}propan-1-ol (500 mg) en tolueno (13 ml) se añadió clorosulfonilisocianato (155 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (248 mg) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se añadió éter 2-aminoetilisopropílico (648 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró

y se concentró. El residuo obtenido se sometió a HPLC (acetonitrilo:agua, con contenido de 0.01% de TFA, 5:95 - 100:0, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}propilo (145 mg, rendimiento: 20%) en forma de cristales incoloros. Punto de fusión 68.0-69.2°C.

Ejemplo 431

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.60 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.14 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.44 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (0.77 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 8:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de (2E)-3-[2-{[3-

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cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.35 g, rendimiento: 38%) en forma de cristales incoloros. Punto de fusión 127-128°C.

Ejemplo 432

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.60 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.14 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.44 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se añadió 3-metoxipropilamina (0.66 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 8:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(3-metoxipropil)amino]sulfonil}carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.42 g, rendimiento: 47%) en forma de cristales incoloros. Punto de fusión 98-100°C.

Ejemplo 433

A una solución de (2E)-3-[2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.60 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.14 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.44 ml) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se añadió 1-pentilamina (0.65 g) y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar [(pentilamino)sulfonil]carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.23 g, rendimiento: 26%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.81 - 0.94 (3 H, m), 1.19 - 1.39 (4 H, m), 1.45 - 1.73 (2 H, m), 2.97 - 3.12 (2 H, m), 3.44 (3 H, s), 3.74 (2 H, dd, J = 5.5, 4.0 Hz), 4.02 - 4.18 (2 H, m), 4.72 (2 H, dd, J = 6.6, 1.1 Hz), 4.91 - 5.05 (1 H, m), 6.09 - 6.26 (1 H, m), 6.58 - 6.71 (2 H, m), 6.83 - 6.94 (1 H, m), 7.13 (1 H, br.s.), 7.48 - 7.56 (1 H, m), 8.01 (1 H, d, J = 1.7 Hz), 8.25 (1 H, dd, J = 2.1, 0.9 Hz).

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Ejemplo 434

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.60 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.14 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.44 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora, se añadió 1-(2-aminoetil)pirrolidina (0.85 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con metanol-acetato de etilo (0:1 - 8:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-pirrolidin-1-iletil)amino]sulfonil}carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.40 g, rendimiento: 43%) en forma de cristales incoloros. Punto de fusión 154-156°C.

Ejemplo 435

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.60 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.14 ml) bajo enfriamiento con hielo,

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y la mezcla se agitó durante 30 min. Se añadió piridina (0.44 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora, fenetilamina (0.90 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 6:4, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-feniletil)amino]sulfonil}carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.49 g, rendimiento: 53%) en forma de cristales incoloros. Punto de fusión 113-114°C.

Ejemplo 436

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.60 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.14 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.44 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora, se agregó 2-(2-aminoetil)piridina (1.46 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa

de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:8 - 9:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-piridin-2-iletil)amino]sulfonil}carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.43 g, rendimiento: 46%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:3.05 (2 H, J = 6.2 Hz), 3.44 (3 H, s), 3.53 (2 H, t, J = 6.2 Hz), 3.74 (2 H, dd, J = 5.4, 3.9 Hz), 4.05 - 4.15 (2 H, m), 4.67 (2 H, dd, J = 6.4, 0.9 Hz), 6.06 - 6.23 (1 H, m), 6.57 - 6.70 (2 H, m), 6.86 (1 H, dd, J = 8.7, 2.4 Hz), 7.08 - 7.18 (2 H, m), 7.49 (1 H, d, J = 8.9 Hz), 7.54 - 7.66 (1 H, m), 8.00 (1 H, d, J = 2.1 Hz), 8.23 (1 H, d, J = 0.9 Hz), 8.44 - 8.54 (1 H, m).

Ejemplo 437

A una solución de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ol (0.50 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.11 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.37 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora, se agregó pirrolidina (0.44 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h.

Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 6:4, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (pirrolidin-1-ilsulfonil)carbamato de (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]prop-2-en-1-ilo (0.53 g, rendimiento: 73%) en forma de cristales incoloros. Punto de fusión 123-124°C.

Ejemplo 438

A una solución de 3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propan-1-ol (1.00 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.15 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.47 ml) a la mezcla de reacción, la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (0.82 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 -

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1:1, v/v) para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propilo (0.88 g, rendimiento: 66%) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.04 (9 H, s), 1.13 (6 H, d, J = 6.2 Hz), 1.85 - 2.01 (2 H, m), 2.54 (2 H, t, J = 7.4 Hz), 3.16 - 3.29 (2 H, m), 3.44 - 3.63 (3 H, m), 3.89 - 4.20 (6 H, m), 5.39 (1 H, t, J = 5.7 Hz), 6.63 (1 H, d, J = 2.4 Hz), 6.77 (1 H, dd, J = 8.5, 2.6 Hz), 7.17 (1 H, d, J = 8.5 Hz), 7.31 - 7.48 (7 H, m), 7.62 - 7.74 (7 H, m), 8.01 (1 H, d, J = 1.7 Hz), 8.26 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo 439

A una solución de {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(4-(2-{[ter-butil(difenil)silil]oxi}etoxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propilo (0.88 g) en tetrahidrofurano (5 ml) se añadieron una solución en tetrahidrofurano 1.0 M de fluoruro de tetra-n-butilamonio (5.3 ml), y la mezcla se agitó a temperatura ambiente durante 6 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a HPLC (acetonitrilo:agua, con contenido de 0.01% de TFA, 5:95 - 100:0, v/v) para dar {[(2-

isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxietoxi)fenil]propilo (0.32 g, rendimiento: 51%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.2 Hz), 1.88 - 2.00 (2 H, m), 2.01 - 2.13 (1 H, m), 2.58 (2 H, t, J = 7.3 Hz), 3.23 (2 H, q, J = 5.5 Hz), 3.47 - 3.65 (3 H, m), 3.95 (2 H, d, J = 4.1 Hz), 4.03 - 4.19 (4 H, m), 5.39 (1 H, t, J = 5.8 Hz), 6.69 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.5, 2.4 Hz), 7.20 (1 H, d, J = 8.5 Hz), 7.54 (1 H, br.s.), 8.02 (1 H, d, J = 2.3 Hz), 8.25 - 8.31 (1 H, m).

Ejemplo 440

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propan-1-ol (0.40 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.09 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se añadió 3-metoxipropilamina (0.48 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano

(0:1 - 4:6, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(3-metoxipropil)amino]sulfonil}carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propilo (0.44 g, rendimiento: 74%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.33 (6 H, d, J = 6.0 Hz), 1.75 - 2.02 (4 H, m), 2.55 (2 H, t, J = 7.5 Hz), 3.12 - 3.23 (2 H, m), 3.32 (3 H, s), 3.44 - 3.51 (2 H, t, J = 5.6 Hz), 4.15 (2 H, t, J = 6.4 Hz), 4.43 - 4.54 (1 H, m), 5.57 - 5.66 (1 H, m), 6.62 (1 H, d, J = 2.4 Hz), 6.77 (1 H, dd, J = 8.5, 2.6 Hz), 7.17 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 2.1 Hz), 8.28 (1 H, d, J = 1.3 Hz).

Ejemplo 441

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propan-1-ol (0.40 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.09 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (0.56 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió

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a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propilo (0.32 g, rendimiento: 51%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.2 Hz), 1.32 (6 H, d, J = 6.0 Hz), 1.86 - 2.02 (2 H, m), 2.54 (2 H, t, J = 7.3 Hz), 3.23 (2 H, q, J = 5.5 Hz), 3.43 - 3.65 (3 H, m), 4.15 (2 H, t, J = 6.4 Hz), 4.39 - 4.57 (1 H, m), 5.37 (1 H, t, J = 5.7 Hz), 6.62 (1 H, d, J = 2.6 Hz), 6.77 (1 H, dd, J = 8.4, 2.5 Hz), 7.17 (1 H, d, J = 8.5 Hz), 7.37 (1 H, br.s.), 8.00 (1 H, d, J = 2.3 Hz), 8.28 (1 H, d, J = 1.1 Hz).

Ejemplo 442

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propan-1-ol (0.40 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.09 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se añadió 2-fenoxietilamina (0.74 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$)

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y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 3:7, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-fenoxietil)amino]sulfonil}carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propilo (0.30 g, rendimiento: 46%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.0 Hz), 1.79 - 1.98 (2 H, m), 2.53 (2 H, t, J = 7.3 Hz), 3.41 - 3.56 (2 H, m), 4.01 - 4.15 (4 H, m), 4.39 - 4.57 (1 H, m), 5.45 - 5.56 (1 H, m), 6.62 (1 H, d, J = 2.6 Hz), 6.76 (1 H, dd, J = 8.5, 2.4 Hz), 6.82 - 6.90 (2 H, m), 6.92 - 7.01 (1 H, m), 7.14 (1 H, d, J = 8.5 Hz), 7.23 - 7.31 (2 H, m), 7.40 (1 H, br.s.), 8.00 (1 H, d, J = 1.9 Hz), 8.28 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 443

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propan-1-ol (0.40 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.09 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó N-(2-metoxietil)metilamina (0.48 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de

etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 8:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-metoxietil)(metil)amino]sulfonil}carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propilo (0.42 g, rendimiento: 70%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.32 (6 H, d, J = 6.0 Hz), 1.86 - 2.01 (2 H, m), 2.54 (2 H, t, J = 7.4 Hz), 3.00 (3 H, s), 3.36 (3 H, s), 3.44 - 3.61 (4 H, m), 4.12 (2 H, t, J = 6.5 Hz), 4.40 - 4.57 (1 H, m), 6.62 (1 H, d, J = 2.4 Hz), 6.77 (1 H, dd, J = 8.5, 2.4 Hz), 7.17 (1 H, d, J = 8.5 Hz), 7.48 (1 H, br.s.), 8.00 (1 H, d, J = 1.9 Hz), 8.28 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 444

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propan-1-ol (0.40 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.09 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se agregó piridina (0.30 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-(2-aminoetil)piridina (0.66 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente

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durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (0:1 - 8:2, v/v) para dar {[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)propilo (0.33 g, rendimiento: 52%) en forma de un sólido amorfo incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.31 (6 H, d, J = 6.0 Hz), 1.74 - 1.94 (2 H, m), 2.46 (2 H, t, J = 7.4 Hz), 3.03 (2 H, t, J = 6.6 Hz), 3.47 (2 H, t, J = 6.5 Hz), 4.04 (2 H, t, J = 6.3 Hz), 4.36 - 4.57 (1 H, m), 6.60 (1 H, d, J = 2.4 Hz), 6.72 (1 H, dd, J = 8.5, 2.4 Hz), 7.02 - 7.20 (3 H, m), 7.58 (1 H, td, J = 7.7, 1.6 Hz), 7.96 (1 H, d, J = 2.1 Hz), 8.24 (1 H, d, J = 1.1 Hz), 8.47 (1 H, d, J = 4.3 Hz).

Ejemplo 445

A una solución de 2-[2-(benciloxi)-4-(2-metoxietoxi)fenil]etanol (0.30 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.07 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.23 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (0.42 g), y la mezcla se agitó mientras se calentaba hasta

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temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 8:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]etilo (0.26 g, rendimiento: 56%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.13 (6 H, d, J = 6.2 Hz), 2.86 (2 H, t, J = 6.8 Hz), 3.16 (2 H, q, J = 5.7 Hz), 3.43 (3 H, s), 3.46 - 3.64 (3 H, m), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.03 - 4.14 (2 H, m), 4.34 (2 H, t, J = 6.9 Hz), 5.38 (1 H, t, J = 5.8 Hz), 6.66 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.5, 2.6 Hz), 7.23 (1 H, d, J = 8.7 Hz), 7.39 (1 H, br. s.), 8.02 (1 H, d, J = 2.1 Hz), 8.25 - 8.33 (1 H, m).

Ejemplo 446

A una solución de 2-[2-(benciloxi)-4-(2-metoxietoxi)fenil]etanol (0.30 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.07 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.23 ml) se añadió a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-

(aminopropil)isopropílico (0.48 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 8:2, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(3-isopropoxipropil)amino]sulfonil}carbamato de 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]etilo (0.31 g, rendimiento: 66%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.13 (6 H, d, J = 6.2 Hz), 2.86 (2 H, t, J = 6.8 Hz), 3.16 (2 H, q, J = 5.7 Hz), 3.43 (3 H, s), 3.46 - 3.64 (3 H, m), 3.73 (2 H, dd, J = 5.5, 4.0 Hz), 4.03 - 4.14 (2 H, m), 4.34 (2 H, t, J = 6.9 Hz), 5.38 (1 H, t, J = 5.8 Hz), 6.66 (1 H, d, J = 2.4 Hz), 6.83 (1 H, dd, J = 8.5, 2.6 Hz), 7.23 (1 H, d, J = 8.7 Hz), 7.39 (1 H, br.s.), 8.02 (1 H, d, J = 2.1 Hz), 8.25 - 8.33 (1 H, m).

Ejemplo 447

A una solución de 2-[2-(benciloxi)-4-(2-metoxietoxi)fenil]etanol (0.30 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.07 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.23 ml) a la mezcla de reacción, y la mezcla se agitó

durante 1 hora. Se añadió 3-metoxipropilamina (0.36 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 9:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(3-metoxipropil)amino]sulfonil}carbamato de 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]etilo (0.27 g, rendimiento: 60%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.70 - 1.83 (2 H, m), 2.87 (2 H, t, J = 6.8 Hz), 3.09 (2 H, q, J = 6.2 Hz), 3.31 (3 H, s), 3.38 - 3.49 (5 H, m), 3.73 (2 H, dd, J = 5.6, 3.9 Hz), 4.08 (2 H, dd, J = 5.5, 4.0 Hz), 4.35 (2 H, t, J = 6.9 Hz), 5.52 - 5.64 (1 H, m), 6.65 (1 H, d, J = 2.4 Hz), 6.84 (1 H, dd, J = 8.5, 2.6 Hz), 7.20 - 7.25 (1 H, m), 8.02 (1 H, d, J = 2.1 Hz), 8.30 (1 H, d, J = 1.1 Hz).

Ejemplo 448

A una solución de 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]etanol (1.32 g) en acetonitrilo (30 ml) se añadió clorosulfonilisocianato (0.54 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (1.62

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ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (1.98 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 2-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]etilo (0.29 g, rendimiento: 14%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.13 (6 H, d, J = 6.2 Hz), 2.86 (2 H, t, J = 6.8 Hz), 3.18 (2 H, q, J = 5.7 Hz), 3.42 - 3.63 (6 H, m), 4.35 (2 H, t, J = 6.9 Hz), 5.15 (2 H, s), 5.40 (1 H, t, J = 6.0 Hz), 6.80 (1 H, d, J = 2.4 Hz), 6.95 (1 H, dd, J = 8.5, 2.4 Hz), 7.24 (1 H, d, J = 8.5 Hz), 7.37 (1 H, s), 8.01 (1 H, d, J = 1.9 Hz), 8.29 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo 449

A una solución de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}-N-(pentilsulfonil)acrilamida (463 mg) en tetrahidrofurano (4 ml) y metanol (4 ml) se añadió

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óxido de platino (IV) (18 mg), y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 2 h. La mezcla de reacción se filtró y el filtrado se concentró para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio 3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(ciclopropiloxi)etoxi]fenil}-N-(pentilsulfonil)propanamida (395.5 mg, rendimiento: 85%) en forma de cristales blancos.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.43 - 0.54 (2 H, m), 0.55 - 0.63 (2 H, m), 0.90 (3 H, t, J = 7.0 Hz), 1.14 - 1.43 (4 H, m), 1.59 - 1.72 (2 H, m), 2.55 (2 H, t, J = 7.2 Hz), 2.95 (2 H, t, J = 7.2 Hz), 3.10 - 3.21 (2 H, m), 3.36 (1 H, tt, J = 6.1, 3.0 Hz), 3.71 - 3.83 (2 H, m), 3.91 - 4.08 (2 H, m), 6.51 (1 H, d, J = 2.7 Hz), 6.77 (1 H, dd, J = 8.3, 2.7 Hz), 7.18 (1 H, d, J = 8.7 Hz), 8.08 (1 H, d, J = 2.3 Hz), 8.37 (1 H, dd, J = 2.1, 0.9 Hz).

Ejemplo 450

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propan-1-ol (5.2 g) en acetonitrilo (100 ml) se añadió clorosulfonilisocianato (2.1 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (4.1 ml) se añadió a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (6.8 g), y la mezcla se agitó mientras

se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 6:4, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(metoximetoxi)fenil]propilo (5.2 g, rendimiento: 65%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:1.14 (6 H, d, J = 6.0 Hz), 1.88 - 2.01 (2 H, m), 2.56 (2 H, t, J = 7.4 Hz), 3.23 (2 H, q, J = 5.7 Hz), 3.48 (3 H, s), 3.49 - 3.62 (3 H, m), 4.15 (2 H, t, J = 6.4 Hz), 5.15 (2 H, s), 5.39 (1 H, t, J = 5.9 Hz), 6.82 (1 H, d, J = 2.7 Hz), 6.94 (1 H, dd, J = 8.3, 2.7 Hz), 7.20 (1 H, d, J = 8.3 Hz), 7.42 (1 H, br. s.), 8.01 (1 H, d, J = 2.3 Hz), 8.27 (1 H, s).

Ejemplo 451

Una mezcla de clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (1.21 g), 4-dimetilaminopiridina (892 mg), y acetonitrilo (10 ml) se agitó a temperatura ambiente durante 10 min. A la mezcla se añadieron ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-cianopropoxi)fenil]acrílico (2.08 g) y pentan-

1-sulfonamida (749 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. Una solución 1 M de ácido clorhídrico se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-cianopropoxi)fenil]-N-(pentilsulfonil)acrilamida (708 mg, rendimiento: 26%) en forma de cristales incoloros. Punto de fusión 165-166°C.

Ejemplo 452

Una mezcla de clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (150 mg), 4-dimetilaminopiridina (110 mg), y acetonitrilo (3 ml) se agitó a temperatura ambiente durante 10 min. A la mezcla se añadieron ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-oxopropoxi)fenil]acrílico (250 mg) y pentan-1-sulfonamida (93 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. Una solución 1 M de ácido clorhídrico se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-oxopropoxi)fenil]-N-(pentilsulfonil)acrilamida (70 mg,

rendimiento: 30%) en forma de cristales incoloros. Punto de fusión 187-188°C.

Ejemplo 453

Una mezcla de clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (940 mg), 4-dimetilaminopiridina (691 mg), y acetonitrilo (5 ml) se agitó a temperatura ambiente durante 10 min. A la mezcla se añadieron ácido (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}acrílico (1.79 g) y pentan-1-sulfonamida (580 mg), y la mezcla se agitó a temperatura ambiente durante 15 h. Una solución 1 M de ácido clorhídrico se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}-N-(pentilsulfonil)acrilamida (1.19 g, rendimiento: 52%) en forma de cristales incoloros. Punto de fusión 90-92°C.

Ejemplo 454

Una mezcla de (2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-(2-metil-1,3-dioxolan-2-il)etoxi]fenil}-N-(pentilsulfonil)acrilamida (750 mg), solución de ácido clorhídrico 1 M (5 ml), y tetrahidrofurano (15 ml) se agitó a 60°C durante 1 hora. Tras enfriar hasta

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temperatura ambiente, la mezcla se concentró. Se añadió agua al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El sólido obtenido se recristalizó en acetato de etilo para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-oxobutoxi)fenil]-N-(pentilsulfonil)acrilamida (418 mg, rendimiento: 60%) en forma de cristales incoloros. Punto de fusión 180-181°C.

Ejemplo 455

Una mezcla de clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (247 mg), 4-dimetilaminopiridina (182 mg), y acetonitrilo (5 ml) se agitó a temperatura ambiente durante 10 min. A la mezcla se añadieron ácido (2E)-3-(4-[2-(acetiloxi)-3-isopropoxipropoxi]-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)acrílico (513 mg) y pentan-1-sulfonamida (152 mg), y la mezcla se agitó a temperatura ambiente durante 2.5 h. Una solución 1 M de ácido clorhídrico se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5 - 1:2, v/v). El sólido obtenido se recristalizó en éter dietílico-hexano para dar 2-(3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{(1E)-3-oxo-3-

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[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)-1-(isopropoximetil)acetato de etilo (487 mg, rendimiento: 76%) en forma de cristales incoloros. Punto de fusión 101-103°C.

Ejemplo 456

A una mezcla de 2-(3-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)-1-(isopropoximetil)acetato de etilo (380 mg), tetrahidrofurano (6 ml), y etanol (4 ml) se añadió una solución 1 M de hidróxido de sodio (4 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se vertió en agua, y la mezcla se neutralizó con una solución 1 M de ácido clorhídrico (4.1 ml) y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 2:1, v/v). El sólido obtenido se recristalizó en éter dietílico-hexano para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-3-isopropoxipropoxi)fenil]-N-(pentilsulfonil)acrilamida (185 mg, rendimiento: 52%) en forma de cristales incoloros. Punto de fusión 86-88°C.

Ejemplo 457

Una mezcla de ácido (2E)-3-[1-(2,4-diclorobencil)-5-metil-1H-pirrol-2-il]acrílico (600 mg), 1.1'-

carbonildiimidazol (408 mg) y N,N-dimetilformamida (7 ml) se agitó a temperatura ambiente durante 1 hora. A la mezcla se añadieron pentan-1-sulfonamida (336 mg) y 1.8-diazabiciclo[5.4,0]undec-7-eno (0.434 ml), y la mezcla se agitó a 100°C durante 18 h. Después de enfriar, la mezcla de reacción hasta temperatura ambiente, se adicionó una solución 1 M de ácido clorhídrico, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:4 - 99:1, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-5-metil-1H-pirrol-2-il]-N-(pentilsulfonil)acrilamida (545 mg, rendimiento: 64%) cristales de color naranja. Punto de fusión 189-190°C.

Ejemplo 458

Una mezcla de clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (498 mg), 4-dimetilaminopiridina (367 mg), y acetonitrilo (5 ml) se agitó a temperatura ambiente durante 10 min. A la mezcla se añadieron ácido (2E)-3-[1-(2,4-diclorobencil)-3.5-dimetil-1H-pirrol-2-il]acrílico (650 mg) y pentan-1-sulfonamida (308 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Una solución 1 M de ácido clorhídrico se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa

de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:5 - 1:3, v/v). El sólido obtenido se recristalizó en acetato de etilo-hexano para dar (2E)-3-[1-(2,4-diclorobencil)-3.5-dimetil-1H-pirrol-2-il]-N-(pentilsulfonil)acrilamida (481 mg, rendimiento: 53%) en forma de cristales de color amarillo pálido. Punto de fusión 170-171°C.

Ejemplo 459

A una mezcla de ácido (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]acrílico (989 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (682 mg), 4-dimetilaminopiridina (522 mg) y acetonitrilo (4.7 ml) se añadió pentan-1-sulfonamida (358 mg) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 16 h, se añadieron ácido clorhídrico 1 N (6 ml), acetato de etilo (15 ml) y agua (6 ml) sucesivamente, y la mezcla se agitó a temperatura ambiente durante 10 min. La capa orgánica se separó y la capa acuosa se extrajo con acetato de etilo (8 ml). La capa orgánica combinada se lavó sucesivamente con ácido clorhídrico 1 N (4 ml) y salmuera saturada (4 ml), y se secó ($MgSO_4$). El solvente se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de

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sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se disolvieron en acetato de etilo, se añadió hexano y la mezcla se dejó en reposo durante 1.5 h. También se agregó hexano (1.5 ml), y la mezcla se agitó durante 1.5 h. Los cristales precipitados se recogieron por filtración con hexano para dar (2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]N-(pentilsulfonil)acrilamida (806 mg, rendimiento: 62%) en forma de cristales incoloros. Los cristales obtenidos se recristalizaron en etanol para dar cristales incoloros. Punto de fusión 123-125°C.

^{1}H-RMN (300 MHz, $CDCl_3$)δ:0.88 (3 H, t, J = 7.1 Hz), 1.24 - 1.50 (4 H, m), 1.72 - 1.91 (2 H, m), 3.39 - 3.53 (5 H, m), 3.75 (2 H, dd, J = 5.3, 3.8 Hz), 4.14 (2 H, dd, J = 5.4, 3.7 Hz), 6.37 (1 H, d, J = 15.6 Hz), 6.70 (1 H, d, J = 2.5 Hz), 6.90 (1 H, dd, J = 8.7, 2.5 Hz), 7.60 (1 H, d, J = 8.7 Hz), 7.80 (1 H, d, J = 15.6 Hz), 8.01 (1 H, s), 8.03 (1 H, d, J = 2.3 Hz), 8.19 - 8.30 (1 H, m).

Ejemplo 460

A una solución de ácido (2E)-3-[2-[(5-bromo-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]acrílico (697 mg) en acetonitrilo (15 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (709 mg), trietilamina (524 mg), 4-dimetilaminopiridina (234 mg) y pentan-1-sulfonamida (286 mg), y la mezcla se agitó a temperatura ambiente durante 40 h. Una

solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en etanol-hexano para dar (2E)-3-[2-[(5-bromo-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (765 mg, rendimiento: 83%) en forma de cristales incoloros. Punto de fusión 159.8-160.2°C.

Ejemplo 461

A una solución de ácido (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-2-metoxiacrílico (450 mg) en acetonitrilo (10 ml) se añadieron anhídrido 2-metil-6-nitrobenzoico (404 mg), trietilamina (300 mg), 4-dimetilaminopiridina (118 mg) y pentan-1-sulfonamida (164 mg), y la mezcla se agitó a temperatura ambiente durante 20 h. Una solución acuosa saturada de cloruro de amonio se vertió en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3, v/v) para dar (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-2-metoxi-N-(pentilsulfonil)acrilamida

(300 mg, rendimiento: 51%) como un sólido amorfo.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.89 (3 H, t, J = 7.0 Hz), 1.25 - 1.45 (4 H, m), 1.79 - 1.88 (2 H, m), 2.01 - 2.09 (2 H, m), 3.34 (3 H, s), 3.42 - 3.49 (2 H, m), 3.54 (2 H, t, J = 6.1 Hz), 3.66 (3 H, s), 4.08 (2 H, t, J = 6.1 Hz), 6.71 (1 H, d, J = 2.7 Hz), 6.90 (1 H, dd, J = 9.1, 2.7 Hz), 7.17 (1 H, s), 7.91 (1 H, d, J = 9.1 Hz), 8.00 (1 H, d, J = 1.9 Hz), 8.21 (1 H, s), 8.65 (1 H, s).

Ejemplo 462

A una solución de [6-(5-(2-metoxietoxi)-2-{(1E)-3-oxo-3-[(pentilsulfonil)amino]prop-1-en-1-il}fenoxi)-5-metilpiridin-3-il]carbamato de ter-butilo (327 mg) en metanol (3 ml) se añadió solución metanólica al 10% de cloruro de hidrógeno (3 ml), y la mezcla se agitó a temperatura ambiente durante 14 horas y luego a 45°C durante 3 h. La mezcla de reacción se concentró, y los cristales crudos obtenidos se recristalizaron en metanol-éter diisopropílico para dar diclorhidrato de (2E)-3-[2-[(5-amino-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (207 mg, rendimiento: 66%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, DMSO-d_6) δ:0.80 - 0.85 (3 H, m), 1.14 - 1.29 (4 H, m), 1.30 - 1.49 (2 H, m), 2.39 (3 H, s), 3.09 - 3.27 (4 H, m), 3.30 (3 H, s), 3.65 - 3.67 (2H, m), 4.13 - 4.16 (2 H, m), 6.21 - 6.24 (1 H, m), 6.96 (1 H, dd, J = 8.7, 2.4 Hz), 7.05 (1 H, d, J = 2.4 Hz), 7.39 (1 H, d, J = 8.7 Hz),

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7.66 - 7.67 (2 H, m), 11.93 (1 H, s).

Ejemplo 463

A una solución de diclorhidrato de (2E)-3-[2-[(5-amino-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (321 mg) en piridina (5 ml) se añadieron anhídrido acético (445 mg) y 4-dimetilaminopiridina (145 mg), y la mezcla se agitó a temperatura ambiente durante 7 h. La mezcla de reacción se concentró, se añadió una solución acuosa saturada de cloruro de amonio al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo. Los cristales crudos obtenidos se recristalizaron en etanol-hexano para dar (2E)-3-[2-{[5-(acetilamino)-3-metilpiridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (150 mg, rendimiento: 49%) en forma de cristales incoloros. Punto de fusión 187.9-188.2°C.

Ejemplo 464

A una solución de diclorhidrato de (2E)-3-[2-[(5-amino-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (356 mg) en piridina (5 ml) se añadieron cloruro de metansulfonilo (398 mg) y 4-dimetilaminopiridina (132 mg), y la mezcla se agitó a

temperatura ambiente durante 8 h. La mezcla de reacción se concentró, se añadió agua al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-[2-({5-[bis(metilsulfonil)amino]-3-metilpiridin-2-il}oxi)-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (100 mg, rendimiento: 24%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:0.88 (3 H, t, J = 7.1 Hz), 1.25 - 1.41 (4 H, m), 1.75 - 1.88 (2 H, m), 2.44 (3 H, s), 3.40 (6 H, s), 3.43 (3 H, s), 3.43 - 3.45 (2 H, m), 3.72 - 3.75 (2 H, m), 4.11 - 4.14 (2 H, m), 6.28 (1 H, d, J = 15.7 Hz), 6.67 (1 H, d, J = 2.5 Hz), 6.84 (1 H, dd, J = 8.7, 2.5 Hz), 7.53 - 7.56 (2 H, m), 7.82 (1 H, d, J = 15.7 Hz), 7.91 (1 H, d, J = 2.5 Hz), 8.10 (1 H, s).

Ejemplo 465

A una solución de (ciclopropilmetil)carbamato de 3-[2-hidroxi-4-(2-metoxietoxi)fenil]propilo (470 mg) en N,N-dimetilformamida (6 ml) se añadieron 5.6-dicloronicotinato de etilo (476 mg) y carbonato de potasio (503 mg), y la mezcla se agitó a 80°C durante 1 hora. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de

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etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:2, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo - hexano para dar 5-cloro-6-[2-[3-({[(ciclopropilmetil)amino]carbonil}oxi)propil]-5-(2-metoxietoxi)fenoxi]nicotinato de etilo (698 mg, rendimiento: 95%) en forma de cristales incoloros. Punto de fusión 94.6-94.8°C.

Ejemplo 466

A una solución mixta de 5-cloro-6-[2-[3-({[(ciclopropilmetil)amino]carbonil}oxi)propil]-5-(2-metoxietoxi)fenoxi]nicotinato de etilo (297 mg) en tetrahidrofurano (3 ml) y etanol (3 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (1.2 ml), y la mezcla se agitó a 60°C durante 1 hora. Tras enfriar, la mezcla de reacción se concentró, y el concentrado se neutralizó con ácido clorhídrico 1 N. Se vertió agua en la mezcla obtenida, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar ácido (2Z)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]-2-metoxiacrílico (270 mg, rendimiento: 96%) en forma de

cristales incoloros. Punto de fusión 139.5-140.8°C.

Ejemplo 467

A una solución de (2E)-3-[2-[(5-bromo-3-metilpiridin-2-il)oxi]-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida (310 mg) en 1.2-dimetoxietano (10 ml) se añadieron dihidroxifenilborano (109 mg), una solución acuosa 2 N de carbonato de sodio (1.2 ml) y tetraquis(trifenilfosfina)paladio (0) (35 mg), y la mezcla se calentó a reflujo durante 24 h. Tras enfriar, se vertió agua en la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (2:3, v/v). Los cristales crudos obtenidos se recristalizaron en acetato de etilo-hexano para dar (2E)-3-{4-(2-metoxietoxi)-2-[(3-metil-5-fenilpiridin-2-il)oxi]fenil}-N-(pentilsulfonil)acrilamida (205 mg, rendimiento: 65%) en forma de cristales incoloros. Punto de fusión 132.8-133.5°C.

Ejemplo 468

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]propan-1-ol (0.30 g) en acetonitrilo (5 ml) se añadió clorosulfonilisocianato (0.11 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió

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piridina (0.21 ml) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (0.38 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 7:3, v/v) y se concentró para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]propilo (0.008 g, 1%) en forma de un sólido incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.06 - 1.17 (6 H, m), 1.33 (3 H, s), 1.55 (3 H, s), 1.87 - 2.01 (2 H, m), 2.57 (2 H, t, J = 7.3 Hz), 3.13 - 3.28 (2 H, m), 3.43 - 3.65 (3 H, m), 3.77 (1 H, s), 4.02 - 4.19 (3 H, m), 4.54 (1 H, br.s.), 5.31 - 5.51 (1 H, m), 6.69 (1 H, t, J = 2.6 Hz), 6.76 - 6.87 (1 H, m), 7.12 - 7.23 (1 H, m), 7.42 - 7.65 (1 H, m), 8.01 (1 H, s), 8.28 (1 H, s).

Ejemplo 469

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]propan-1-ol (0.30 g) en acetonitrilo (5 ml)

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se añadió clorosulfonilisocianato (0.11 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (0.21 ml) se añadió a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó 2-(aminoetil)piridina (0.45 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 12 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 7:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar {[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]propilo (0.043 g, 9%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.54 (6 H, s), 1.78 - 2.00 (2 H, m), 2.43 - 2.61 (2 H, m), 2.93 - 3.12 (2 H, m), 3.40 - 3.60 (2 H, m), 3.93 - 4.19 (4 H, m), 4.37 - 4.62 (2 H, m), 6.42 (1 H, br.s.), 6.66 (1 H, dd, J = 11.7, 2.4 Hz), 6.71 - 6.86 (1 H, m), 7.01 - 7.22 (3 H, m), 7.52 - 7.67 (1 H, m), 7.99 (1 H, t, J = 2.5 Hz), 8.21 - 8.31 (1 H, m), 8.44 - 8.54 (1 H, m).

Ejemplo 470

Se mezclaron ácido (2E)-3-(2-{[3-cloro-5-

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(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (0.30 g), N-[(5-metilpirazin-2-il)metil]sulfamida (0.16 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.17 g), 4-dimetilaminopiridina (0.11 g) y N,N-dimetilformamida (5 ml), y la mezcla se agitó a temperatura ambiente durante 12 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (2:8 - 1:0, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-({[(5-metilpirazin-2-il)metil]amino}sulfonil)acrilamida (0.030 g, 7%) en forma de cristales incoloros. Punto de fusión 126-128°C.

Ejemplo 471

Se mezclaron ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (0.30 g), N-(2-piridin-2-iletil)sulfamida (0.16 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.17 g), 4-dimetilaminopiridina (0.11 g) y N,N-dimetilformamida (5 ml), y la mezcla se agitó a temperatura ambiente durante 12 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de

acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 7:3, v/v), se concentró y se cristalizó en acetato de etilo-hexano para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-{[(2-piridin-2-iletil)amino]sulfonil}acrilamida (0.077 g, 18%) en forma de cristales incoloros. Punto de fusión 121-123°C.

Ejemplo 472

Se mezclaron ácido (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metilacrílico (0.30 g), pirrolidin-1-sulfonamida (0.12 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.17 g), 4-dimetilaminopiridina (0.11 g) y N,N-dimetilformamida (5 ml), y la mezcla se agitó a temperatura ambiente durante 12 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 1:1, v/v) y se concentró para dar (2E)-3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-2-metil-N-(pirrolidin-1-ilsulfonil)acrilamida (0.10 g, 26%) en forma de un sólido amorfo incoloro.

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^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.36 (6 H, d, J = 6.0 Hz), 1.89 (4 H, br.s.), 1.99 - 2.12 (3 H, m), 3.49 (4 H, br.s.), 4.45 - 4.64 (1 H, m), 6.71 (1 H, d, J = 2.3 Hz), 6.84 (1 H, dd, J = 8.7, 2.4 Hz), 7.18 - 7.38 (2 H, m), 7.86 - 8.04 (2 H, m), 8.25 (1 H, d, J = 1.1 Hz).

Ejemplo 473

A una solución de 3-(4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propan-1-ol (465 mg) en tolueno (12 ml) se añadió clorosulfonilisocianato (171 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (273 mg) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se añadió éter 2-aminoetilisopropílico (713 mg), y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 1:1, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(4-butoxi-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propilo (430 mg, rendimiento: 61%) en forma de cristales incoloros. Punto de fusión 91.4-91.6°C.

Ejemplo 474

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propan-1-ol (452 mg) en tolueno (11 ml) se añadió clorosulfonilisocianato (160 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (255 mg) a la mezcla de reacción y la mezcla se agitó durante 1 hora. Se agregó éster 2-aminoetilisopropílico (667 mg), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:3 - 1:1, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(3-metoxipropoxi)fenil]propilo (298 mg, rendimiento: 44%) en forma de cristales incoloros. Punto de fusión 67.4-68.0°C.

Ejemplo 475

A una solución de 3-(4-(but-3-en-1-iloxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propan-1-ol (402 mg) en tolueno (10 ml) se añadió clorosulfonilisocianato (148 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (237 mg) se añadió a la

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mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éster 2-aminoetilisopropílico (619 mg), y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 2:3, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(4-(but-3-en-1-iloxi)-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propilo (399 mg, rendimiento: 65%) en forma de cristales incoloros. Punto de fusión 111.1-113.0°C.

Ejemplo 476

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-furilmetoxi)fenil]propan-1-ol (424 mg) en tolueno (10 ml) se añadió clorosulfonilisocianato (147 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (235 mg) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éster 2-aminoetilisopropílico (614 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se

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sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (3:7 - 1:1, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-furilmetoxi)fenil]propilo (359 mg, rendimiento: 57%) en forma de cristales incoloros. Punto de fusión 118.0-119.8°C.

Ejemplo 477

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-morfolin-4-iletoxi)fenil]propan-1-ol (600 mg) en acetonitrilo (13 ml) se añadió clorosulfonilisocianato (194 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (309 mg) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éster 2-aminoetilisopropílico (807 mg), y la mezcla se agitó a temperatura ambiente durante 60 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (1:1 - 9:1, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-morfolin-4-iletoxi)fenil]propilo (376 mg, rendimiento: 43%) en

forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.13 (6 H, d, J = 6.0 Hz), 1.86 - 2.07 (2 H, m), 2.49 - 2.63 (6 H, m), 2.80 (2 H, t, J = 5.6 Hz), 3.17 - 3.26 (2 H, m), 3.48 - 3.62 (3 H, m), 3.69 - 3.76 (4 H, m), 4.05 - 4.19 (4 H, m), 5.43 (1 H, br. s.), 6.64 - 6.68 (1 H, m), 6.77 - 6.82 (1 H, m), 7.17 (1 H, d, J = 8.7 Hz), 8.01 (1 H, d, J = 1.7 Hz), 8.25 - 8.29 (1 H, m).

Ejemplo 478

A una solución de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]propan-1-ol (383 mg) en tolueno (8.9 ml) se añadió clorosulfonilisocianato (132 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (210 mg) a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éster 2-aminoetilisopropílico (549 mg), y la mezcla se agitó a temperatura ambiente durante 60 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice, y se eluyó con acetato de etilo-hexano (7:13 - 7:3, v/v) para dar cristales incoloros. La recristalización en acetato de etilo-hexano dio {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(tetrahidrofurano-2-ilmetoxi)fenil]propilo (246 mg,

rendimiento: 45%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.13 (6 H, d, J = 6.0 Hz), 1.68 - 1.83 (2 H, m), 1.86 - 2.12 (4 H, m), 2.55 (2 H, t, J = 7.3 Hz), 3.23 (2 H, d, J = 4.3 Hz), 3.44 - 3.62 (3 H, m), 3.76 - 3.96 (4 H, m), 4.14 (2 H, t, J = 6.4 Hz), 4.21 - 4.30 (1 H, m), 5.43 (1 H, d, J = 1.7 Hz), 6.67 (1 H, d, J = 2.4 Hz), 6.82 (1 H, dd, J = 8.5, 2.6 Hz), 7.18 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 2.3 Hz), 8.27 (1 H, dd, J = 2.2, 1.0 Hz).

Ejemplo 479

A una solución de 3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-{2-[(triisopropilsilil)oxi]etoxi}fenil)propan-1-ol (10.9 g) en acetonitrilo (150 ml) se añadió clorosulfonilisocianato (2.95 g) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. Se añadió piridina (5.9 ml) se añadió a la mezcla de reacción, y la mezcla se agitó durante 1 hora. Se agregó éter 2-(aminoetil)isopropílico (10.8 g), y la mezcla se agitó mientras se calentaba hasta temperatura ambiente durante 6 h. Una solución acuosa saturada de carbonato ácido de sodio se añadió a la mezcla de reacción, y la mezcla se concentró. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró.

A una solución del residuo en tetrahidrofurano (100 ml) se añadió una solución en tetrahidrofurano 1.0 M de

fluoruro de tetra-n-butilamonio (100 ml), y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada, se secó ($MgSO_4$) y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice, se eluyó con acetato de etilo-hexano (0:1 - 2:8, v/v), se concentró y se cristalizó en acetato de etilo-hexano. Los cristales obtenidos se sometieron a HPLC (acetonitrilo:agua, con contenido de 0.01% de TFA, 5:95 - 100:0, v/v) y también se cristalizó en acetato de etilo-hexano para dar {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-(4-{2-[(aminosulfonil)oxi]etoxi}-2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}fenil)propilo (0.18 g, 1%) en forma de cristales incoloros.

^{1}H-RMN (300 MHz, $CDCl_3$) δ:1.14 (6 H, d, J = 6.1 Hz), 1.87 - 2.02 (2 H, m), 2.61 (2 H, t, J = 7.0 Hz), 3.16 - 3.27 (2 H, m), 3.48 - 3.64 (3 H, m), 4.11 - 4.18 (2 H, m), 4.23 - 4.32 (2 H, m), 4.52 (2 H, dd, J = 5.3, 3.4 Hz), 4.98 (2 H, br.s.), 5.38 (1 H, t, J = 5.7 Hz), 6.71 (1 H, d, J = 2.7 Hz), 6.82 (1 H, dd, J = 8.7, 2.7 Hz), 7.22 (1 H, d, J = 8.7 Hz), 7.77 (1 H, s), 8.03 (1 H, d, J = 2.3 Hz), 8.28 (1 H, s).

Ejemplo Experimental 1

Acción reductora de glucosa sanguínea y lípidos sanguíneos (triglicéridos) en ratones

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El compuesto de prueba se mezcló con una dieta en polvo (CE-2, CLEA JAPAN, INC.) en una proporción de 0.01% (0.03% para los compuestos de los Ejemplos 1, 2, 12, 81, 94, 96, 129 y 143, y 0.005% para los compuestos de los Ejemplos 28, 30 y 37) y se proveyeron libremente a ratones KKAy (de 9 a 14 semanas de edad, 5 ratones por grupo) que son modelos de diabetes no dependientes de insulina con obesidad (diabetes de tipo 2), durante 4 a 7 días. Durante este periodo, se dio agua libremente. Se extrajo sangre del plexo venoso orbital. Se cuantificaron la glucosa y los triglicéridos en plasma separado de la sangre con Wako Glu2 Tipo L (Wako Pure Chemical Industries, Ltd.) y Wako TG · H Tipo L (Wako Pure Chemical Industries, Ltd.), respectivamente, de acuerdo con un método enzimático. Los resultados se muestran en la Tabla 1.

En la Tabla, la "acción hipoglicémico (%)" muestra un valor relativo (%) del nivel de glucosa sanguínea del grupo de administración del compuesto de prueba cuando el nivel de glucosa sanguínea del grupo sin administración del compuesto de prueba es del 100%. Además, la "acción hipolipidémica (%)" muestra un valor relativo (%) de los triglicéridos sanguíneos del grupo de administración del compuesto de prueba cuando el valor de triglicéridos sanguíneos del grupo sin administración del compuesto de prueba es del 100%.

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Tabla 1

Compuesto de prueba (Ejemplo No.)	acción hipoglicémica (%)	acción hipolipidémica (%)
1	47	53
2	50	41
12	46	43
26	50	62
28	52	32
30	47	57
37	68	70
58	64	73
81	44	60
94	48	79
96	53	57
97	58	64
112	53	70
129	45	76
143	47	76
151	59	73
155	70	70
183	48	44
196	54	79
197	58	87

1234

198	62	84
204	52	36
205	54	50
207	54	43
208	70	71
210	58	69
211	49	46
214	56	65
218	81	129
250	78	121
252	46	20
424	70	18
429	51	60
430	45	34
437	45	58
439	49	34
444	55	52

Tal como se mostró con anterioridad, es obvio que el compuesto de la presente invención tiene superior acción hipoglicémico y acción hipolipidémica, y es útil como agente para la prevención o tratamiento de diabetes, hiperlipidemia (particularmente, hipertrigliceridemia), deterioro de la tolerancia a la glucosa, y similares.

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Ejemplo Experimental 2 (actividad de ligando de heterodímeros PPARγ-RXRα)

Las células PPARγ:RXRα:4ERPP/CHO-K1 descritas en WO03/099793 se cultivaron en medio HamF12 [fabricado por Life Technologies, Inc., US] que contienen 10% de suero bovino fetal [fabricado por Life Technologies, Inc., US], sembradas en una placa blanca de 96 cavidades [fabricada por Corning Coster Corporation, US] a 1×10^4 células/cavidad, y se incubaron durante la noche en una incubadora con gas dióxido de carbono a 37°C.

Luego se extrajo el medio de la placa blanca de 96 cavidades, se agregaron 45 µl de medio HamF12 que contiene 0.1% de albúmina sérica bovina libre de ácidos grasos (BSA) y un compuesto de prueba (5 µl), y Las células se incubaron durante un día en una incubadora con gas dióxido de carbono a 37°C. Se extrajo el medio, se agregó 20 µl de PicaGene7.5 (fabricado por Wako Pure Chemical Industries, Ltd.) diluido dos veces con HBSS (HANKS' BALANCED SALT SOLUTION) [fabricado por BIO WHITTAKER, US]. Después de agitar, se determinó la actividad de luciferasa mediante el contador 1420 ARVO Multilabel [fabricado por PerkinElmer, US].

La tasa de inducción se calculó a partir de la actividad de luciferasa de cada compuesto de prueba en base a la actividad de luciferasa del grupo sin administración del compuesto de prueba como 1. La concentración del compuesto de

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prueba y la tasa de inducción se analizaron con PRISM [fabricado por GraphPad Software, Inc., US] para calcular el valor EC_{50} (concentración de compuesto que muestra 50% del valor máximo de tasa de inducción) del compuesto de prueba. Los resultados se muestran en la Tabla 2.

Tabla 2

compuesto de prueba (Ejemplo No.)	EC_{50} (nM)
1	1.5
2	2.6
12	15
13	26
26	4.6
28	4.5
30	3.8
32	6.6
37	21
44	6.9
47	3.4
51	20
58	10
64	8.7
81	16
94	20

123+

96	8.4
97	7.5
111	9.3
112	8.3
129	10
151	7.2
155	12
173	9.8
183	3.8
190	15
196	4.4
197	28
198	7.8
199	13
204	0.92
205	3.1
207	0.99
208	4.0
209	2.3
210	6.7
211	5.2
214	1.1
218	80
223	55
224	16

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225	16
226	8.5
248	18
250	7.2
251	7.4
252	3.1
255	3.9
256	13
257	2.1
258	1.1
371	4.7
424	6.2
427	22
429	3.8
430	0.95
437	54
439	1.8
444	3.4
446	13
451	15
453	7.3

Tal como se mostró con anterioridad, es obvio que el compuesto de la presente invención tiene superior actividad de ligando del heterodímero PPARγ-RXRα.

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Ejemplo de formulación 1 (producción de cápsula)

1) compuesto del Ejemplo 1	30 mg
2) celulosa en polvo finamente dividida	10 mg
3) lactosa	19 mg
4) estearato de magnesio	1 mg
total	60 mg

1), 2), 3) y 4) se mezclan y se llenan en una cápsula de gelatina.

Ejemplo de Formulación 2 (producción de comprimido)

1) compuesto del Ejemplo 1	30 g
2) lactosa	50 g
3) almidón de maíz	15 g
4) carboximetilcelulosa de calcio	44 g
5) estearato de magnesio	1 g
1000 comprimidos total	140 g

La cantidad total de 1), 2), 3) y 30 g de 4) se amasaron con agua, se secaron al vacío y se les dio forma. El polvo formado se mezcló con 14 g de 4) y 1 g de 5) y la mezcla se procesó con una máquina compresora. De esta manera, se obtuvieron 1000 comprimidos que contenían 30 mg del compuesto del Ejemplo 1 por comprimido.

APLICACION INDUSTRIAL

El compuesto de la presente invención es útil como

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agente para la prevención o tratamiento de diabetes, que se asocia con menor cantidad de efectos secundarios, tales como aumento de peso corporal, acumulación de adipocitos, hipertrofia cardiaca y similares.

La presente solicitud se basa en la solicitud de patente No. 2005-232646 presentada en Japón, cuyos contenidos se incorporan en su totalidad a la presente como referencia.

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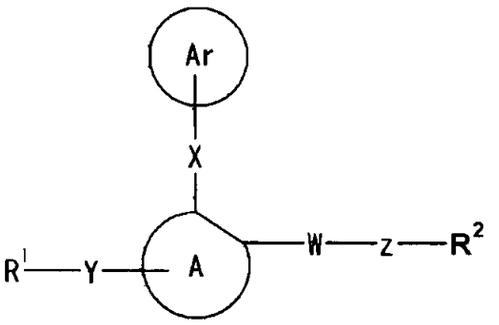
REIVINDICACIONES

1.- Un agente para la prevención o el tratamiento de diabetes, caracterizado porque comprende un compuesto representado por la fórmula:



(I)

en donde el anillo A es un anillo aromático que está además opcionalmente sustituido;

Ar es un anillo monocíclico opcionalmente sustituido;

R^1 es un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido;

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido;

X es un espaciador que tiene una cadena principal de 1 ó 2 átomos;

Y es un enlace o un espaciador con una cadena principal de 1 ó 2 átomos;

W es un grupo hidrocarburo divalente opcionalmente sustituido con 1 a 20 átomos de carbono;

Z es $-CONR^aSO_2-$, $-SO_2NR^aCO-$, $-SO_2NR^aCOO-$, $-NR^aSO_2-$,

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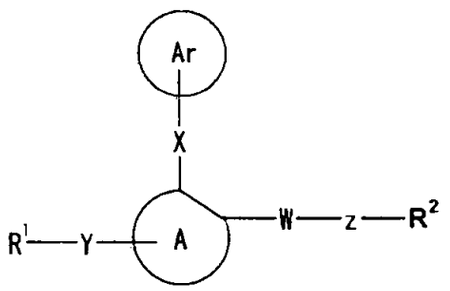
$-OCONR^aSO_2-$, $-OCONR^aSO_2NR^c-$, $-OCONR^c-$, $-NR^aCONR^bSO_2-$, $-NR^aSO_2NR^bCOO-$ o $-CONR^aSO_2NR^c-$ (R^a y R^b son cada uno, de manera independiente, un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, R^c es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, o R^c y R^2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo opcionalmente sustituido con contenido de nitrógeno),

o una de sus sales o uno de sus profármacos.

2.- Un sensibilizador de insulina caracterizado porque comprende el compuesto de conformidad con la reivindicación 1 o una de sus sales o uno de sus profármacos.

3.- El agente de conformidad con la reivindicación 1, caracterizado porque Ar es un anillo aromático monocíclico opcionalmente sustituido.

4.- Un compuesto representado por la fórmula:



(I)

en donde el anillo A, Ar, R^1, R^2, X, Y, W, Z son de conformidad con la reivindicación 1 (con la condición de que Ar no sea un anillo benceno no sustituido),

o una de sus sales, caracterizado porque excluye los siguientes compuestos:

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Ácido (4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acético,

(4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acetato de etilo,

[4-(dietilamino)-2-metilfenil]carbamato de 1-{4-metoxi-2-[(4-vinilbencil)oxi]fenil}etilo,

N-{2-[4.5-dimetoxi-2-(2-tienilcarbonil)fenil]etil}-N,4-dimetilbencensulfonamida,

N-(2.2-dimetoxietil)-N-{3-[6-({(2.2-dimetoxietil)[(4-metilfenil)sulfonil]amino}metil)-2.3-dimetoxifenoxi]-4-metoxibencil}-4-metilbencensulfonamida, y

Fenilcarbamato de 2-[2-(3.4-dimetoxifenil)etil]-4.5-dimetoxibencilo.

5.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Ar es un anillo aromático monocíclico opcionalmente sustituido, o una de sus sales.

6.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Ar es un heterociclo aromático monocíclico de 5 ó 6 miembros opcionalmente sustituido, o una de sus sales.

7.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Ar es un anillo benceno sustituido, o una de sus sales.

8.- El compuesto de conformidad con la

reivindicación 4, caracterizado porque X es un átomo de oxígeno, o una de sus sales.

9.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Z es $-CONR^aSO_2-$, o una de sus sales.

10.- El compuesto de conformidad con la reivindicación 4, caracterizado porque R^1 es

(1) un grupo alquilo de C_{1-10} o un grupo alquenilo de C_{2-10}, cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

un grupo alcoxi de C_{1-6} opcionalmente sustituido con un grupo alcoxi de C_{1-6};

un grupo carbamoilo opcionalmente mono- o disustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico aromático opcionalmente sustituido con un grupo alquilo de C_{1-6};

un grupo heterocíclico no aromático opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

un grupo alcoxi de C_{1-6}-carbonilo;

un grupo carboxilo;

un grupo hidroxi;

un grupo ciano;

un grupo sililoxi opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un

grupo arilo de C_{6-14};

un grupo alquil de C_{1-6}-carboniloxi;

un grupo cicloalquiloxi de C_{3-10};

un grupo cicloalquil de C_{3-10}-alquiloxi de C_{1-6};

un grupo alquilsulfonilo de C_{1-6};

un grupo alquil de C_{1-6}-carbonilo; y

un grupo sulfamoiloxi;

(2) un grupo cicloalquilo de C_{3-10};

(3) un grupo arilo de C_{6-14};

(4) un grupo aralquilo de C_{7-13};

(5) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6};

(6) un grupo heterocíclico no aromático monocíclico; o

(7) un grupo heterocíclico aromático monocíclico, o una de sus sales.

11.- El compuesto de conformidad con la reivindicación 4, caracterizado porque R^2 es

(1) un átomo de hidrógeno;

(2) un grupo alquilo de C_{1-10} o un grupo alquenilo de C_{2-10}, cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6}; un átomo de halógeno; un grupo hidroxi; un grupo ciano; un grupo alquiltio de C_{1-6}; un grupo carbamoilo; un grupo ariloxi de C_{6-14}; un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de un grupo alquilo de C_{1-6}, un grupo alquil de C_{1-6}-carbonilo y

un grupo arilo de C_{6-14}; un grupo heterocíclico aromático opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6}; y un grupo heterocíclico no aromático opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo oxo;

(3) un grupo cicloalquilo de C_{3-10} opcionalmente sustituido con un grupo alquilo de C_{1-6} y opcionalmente condensado con un anillo benceno;

(4) un grupo arilo de C_{6-14} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, un grupo hidroxi, un grupo alcoxi de C_{1-6}, un átomo de halógeno, un grupo nitro, y un grupo ciano;

(5) un grupo aralquilo de C_{7-13} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alcoxi de C_{1-6} y un grupo arilo de C_{6-14};

(6) un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6}; o

(7) un grupo heterocíclico no aromático opcionalmente sustituido con un grupo oxo, o una de sus sales.

12.- El compuesto de conformidad con la reivindicación 4, caracterizado porque el anillo A es un anillo benceno o un heterociclo aromático de 5 ó 6 miembros, o una de sus sales.

13.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Y es un enlace, -O- o -

SO_2-, o una de sus sales.

14.- El compuesto de conformidad con la reivindicación 4, caracterizado porque W es alquileno de C_{1-6} o alquenileno de C_{2-6}, o una de sus sales.

15.- El compuesto de conformidad con la reivindicación 4, caracterizado porque es

3-(2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-isopropoxifenil)-N-(pentilsulfonil)propanamida,

(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-(pentilsulfonil)acrilamida,

(pentilsulfonil)carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo,

3-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]-N-(pentilsulfonil)propanamida,

3-{3-ter-butil-1-[2-cloro-4-(trifluorometil)bencil]-1H-pirazol-5-il}-N-(pentilsulfonil)propanamida,

({2-[3-butoxi-1-(2,4-diclorobencil)-1H-pirazol-5-il]etil}sulfonil)carbamato de butilo,

(2E)-3-{2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-[2-etoxi-1-(etoximetil)etoxi]fenil}-N-(pentilsulfonil)acrilamida,

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo,

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{[(2-piridin-2-iletil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]propilo,

3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-metoxietoxi)fenil]-N-[(pentilamino)sulfonil]propanamida,

(2E)-3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxi-2-metilpropoxi)fenil]-N-(pentilsulfonil)acrilamida o

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[2-{[3-cloro-5-(trifluorometil)piridin-2-il]oxi}-4-(2-hidroxietoxi)fenil]propilo,

o una de sus sales.

16.- Un profármaco caracterizado porque es el compuesto de conformidad con la reivindicación 4 o una de sus sales.

17.- Un agente farmacéutico caracterizado porque comprende el compuesto de conformidad con la reivindicación 4 o una de sus sales o uno de sus profármacos.

18.- Un método para la prevención o el tratamiento de diabetes en un mamífero, caracterizado porque comprende la administración del compuesto de conformidad con la reivindicación 1 o una de sus sales o uno de sus profármacos al mamífero.

19.- Un método para mejorar la resistencia a la insulina en un mamífero, caracterizado porque comprende la

administración del compuesto de conformidad con la reivindicación 1 o una de sus sales o uno de sus profármacos al mamífero.

20.- Uso del compuesto de conformidad con la reivindicación 1 o una de sus sales o uno de sus profármacos para la producción de un agente para la prevención o el tratamiento de diabetes.

21.- Uso del compuesto de conformidad con la reivindicación 1 o una de sus sales o uno de sus profármacos para la producción de un sensibilizador de insulina.

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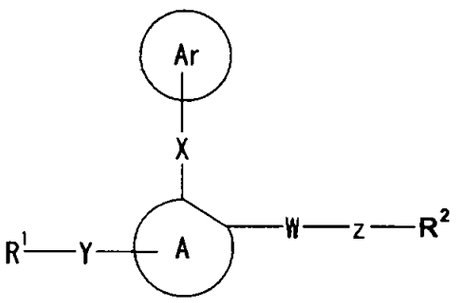
RESUMEN DE LA INVENCION

La presente invención provee un agente para la prevención o el tratamiento de diabetes, que está asociado con menor cantidad de efectos secundarios tales como aumento de peso corporal, acumulación de adipocitos, hipertrofia cardíaca y similares, y que contiene un compuesto representado por la fórmula:



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en donde cada símbolo es como se define en la especificación, o una de sus sales o uno de sus profármacos.

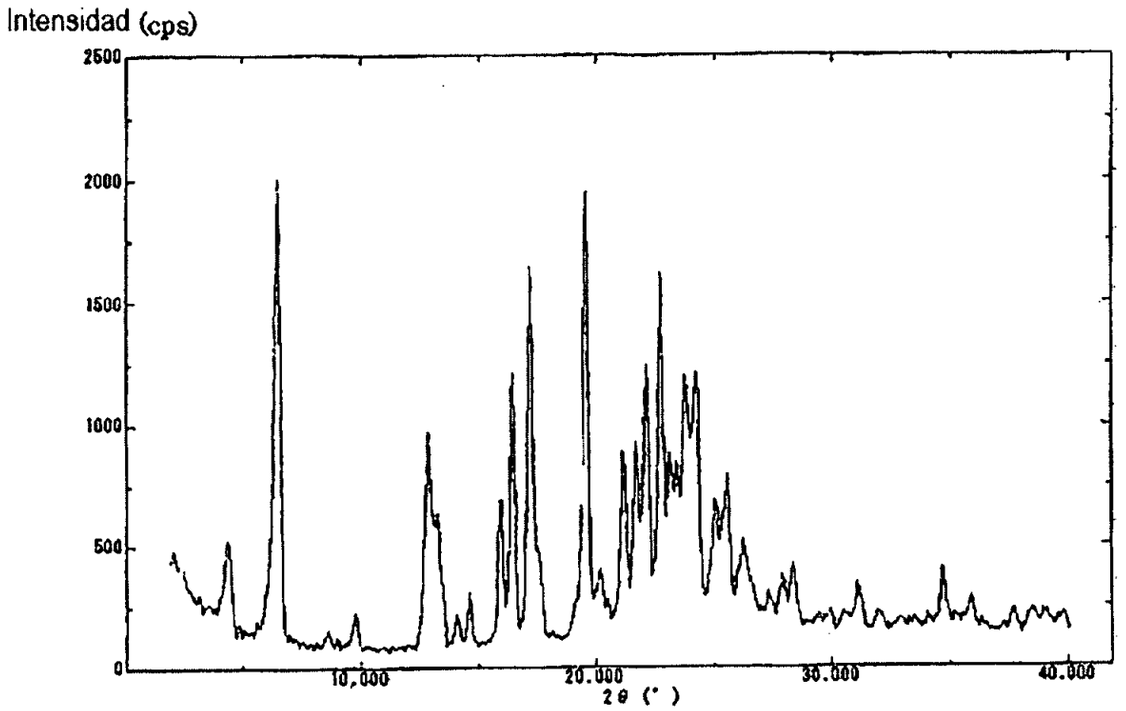
Intensidad (cps)
2500
2000
1500
1000
500
0
10.000
20.000
30.000
40.000
2θ (°)

FIG. 1

1252

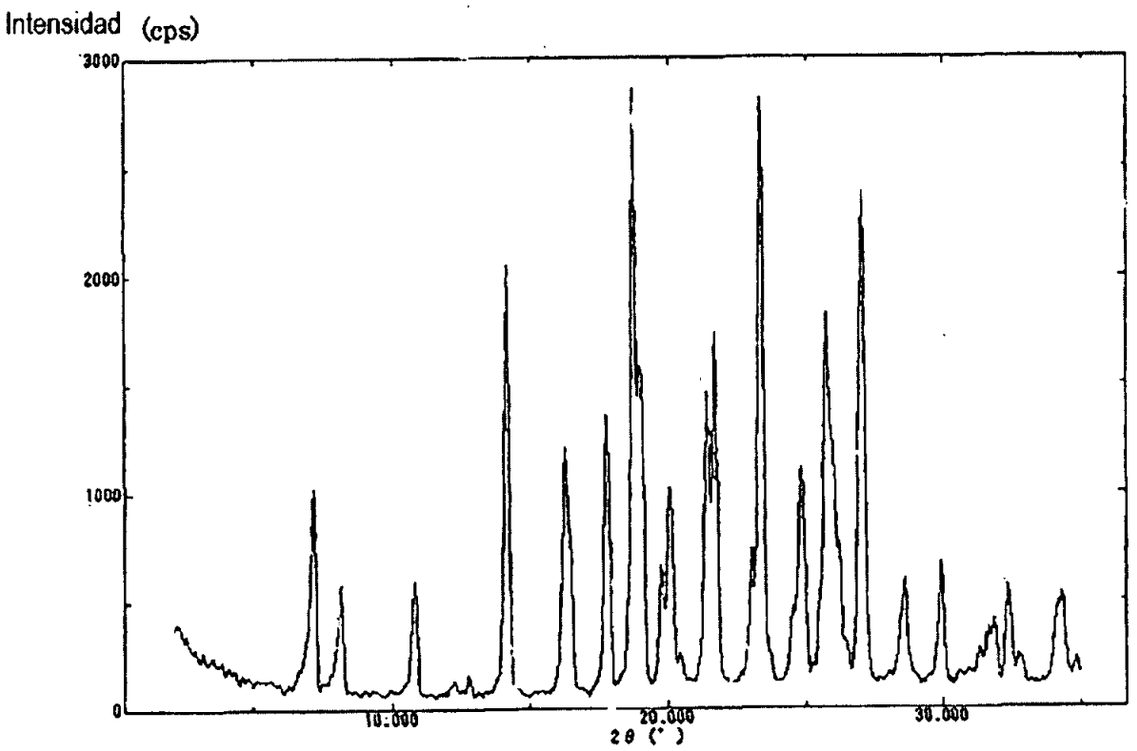

FIG. 2

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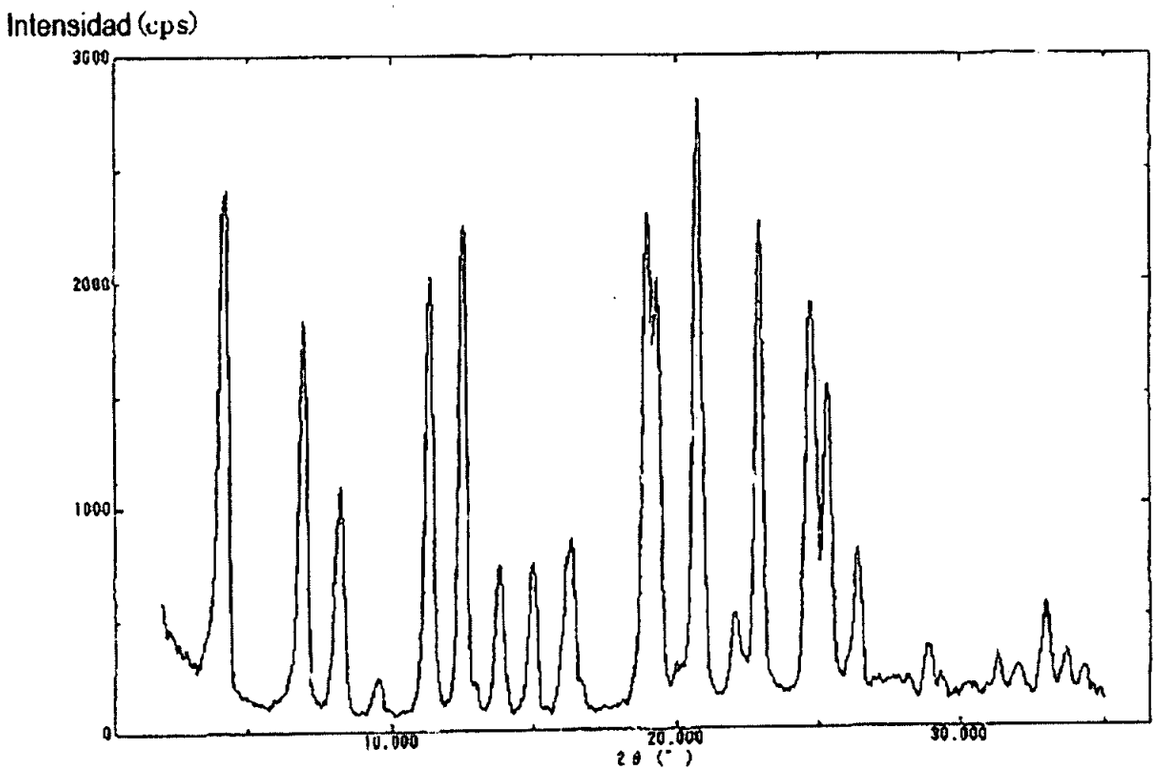

FIG. 3

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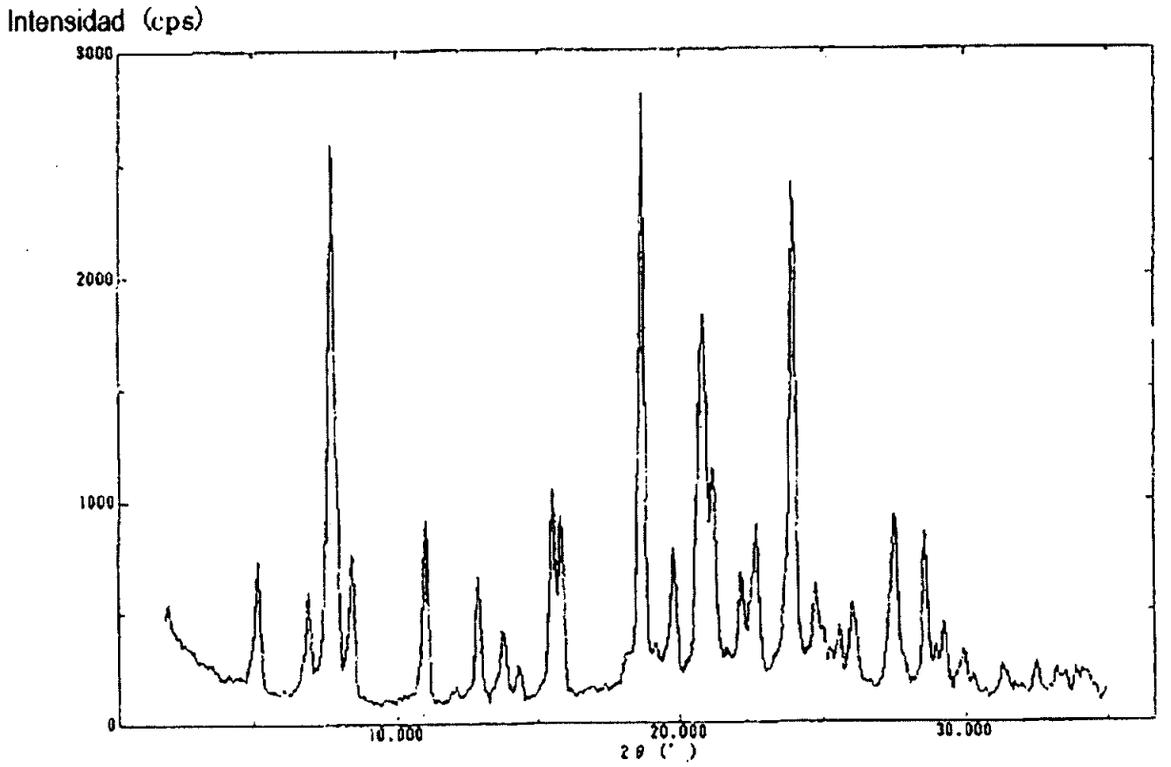

FIG. 4

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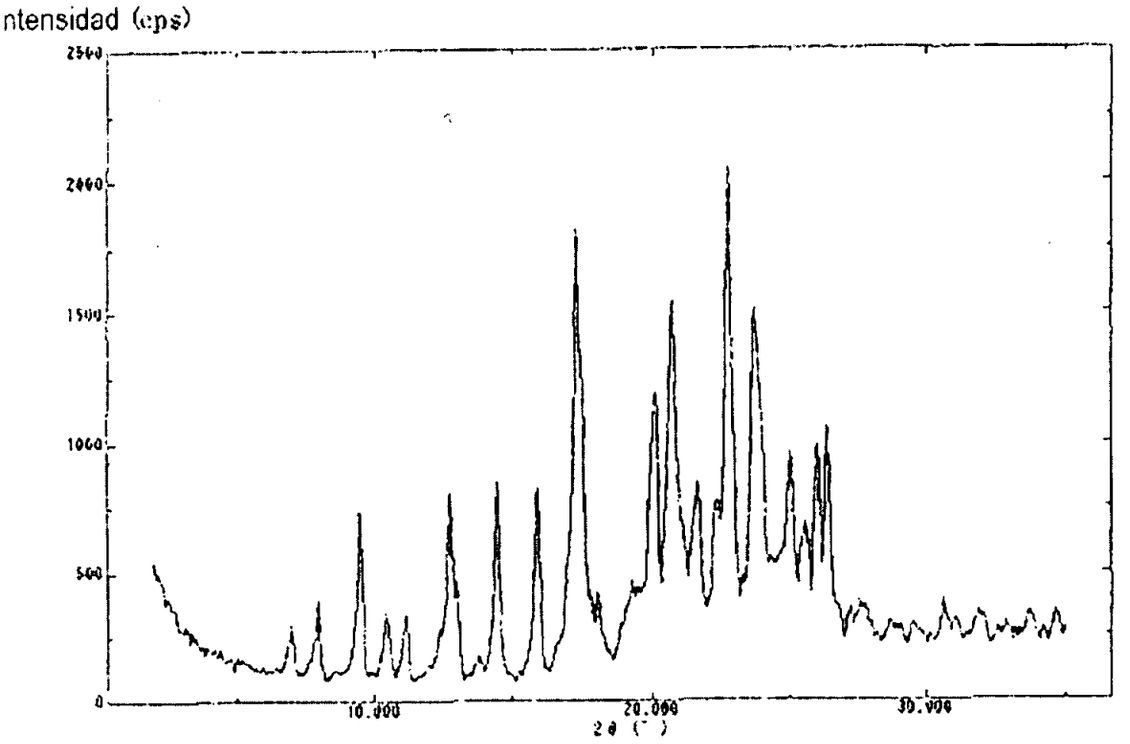
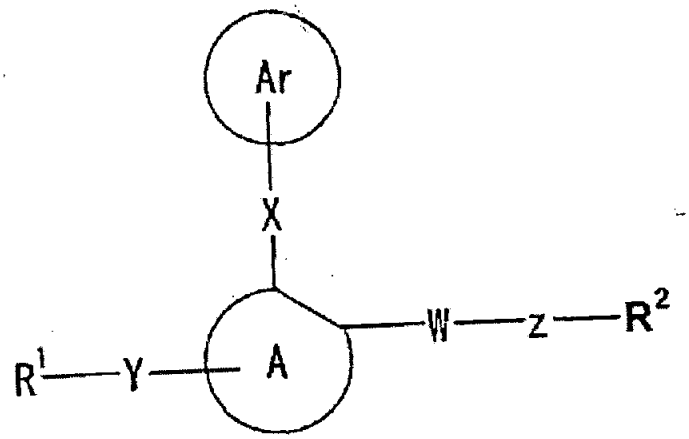


FIG. 5



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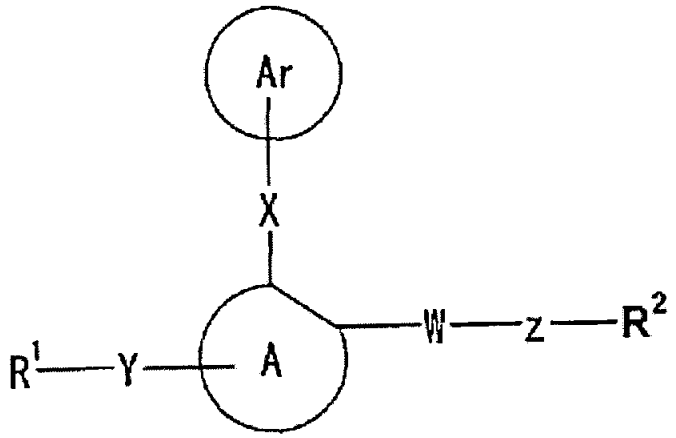

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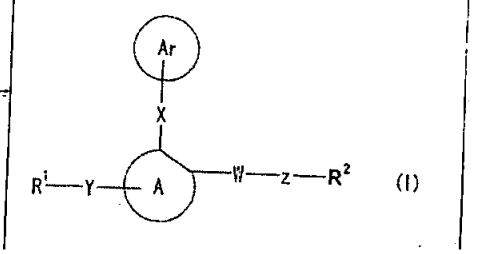

(I)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
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Y OTROS

(74) Apoderado: **EMILIO FERRERO**

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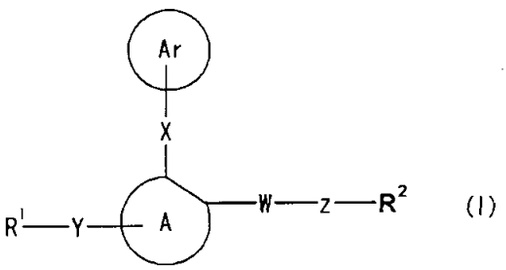
Fecha: 15/02/2007
N° publicación: ***WO 2007/018314 A3***

(54) Titulo: **AGENTE TERAPEUTICO PARA DIABETES**

Reivindicación(es):

1.- Un agente para la prevención o el tratamiento de diabetes, caracterizado porque comprende un compuesto representado por la fórmula:



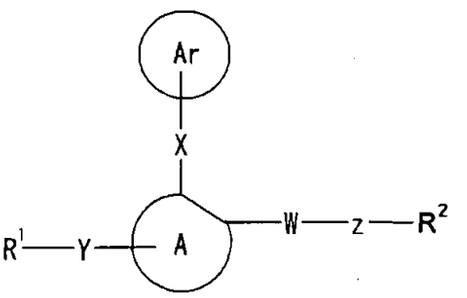
(I)

en donde el anillo A es un anillo aromático que está además opcionalmente sustituido;
Ar es un anillo monociclico opcionalmente sustituido;
R^1 es un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido;
R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o es un grupo heterocíclico opcionalmente sustituido;
X es un espaciador que tiene una cadena principal de 1 ó 2 átomos;
Y es un enlace o un espaciador con una cadena principal de 1 ó 2 átomos;
W es un grupo hidrocarburo divalente opcionalmente sustituido con 1 a 20 átomos de carbono;
Z es -CONRaSO2-, -SO2NRaCO-, -SO2NRaCOO-, -NRaSO2-, -OCONRaSO2-, OCONRaSO2NRc-, -OCONRc-,-NRaCONRbSO2-, -NRaSO2NRbCOO- o -CONRaSO2NRc-(Ra y Rb son cada uno, de manera independiente, un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, Rc es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo protector amino, o Rc y R2 están unidos entre sí para formar, junto con el átomo de nitrógeno adyacente, un heterociclo opcionalmente sustituido con contenido de nitrógeno),
o una de sus sales o uno de sus profármacos.

2.- Un sensibilizador de insulina caracterizado porque comprende el compuesto de conformidad con la reivindicación 1 o una de sus sales o uno de sus profármacos.

3.- El agente de conformidad con la reivindicación 1, caracterizado porque Ar es un anillo aromático monocíclico opcionalmente sustituido.

4.- Un compuesto representado por la fórmula:



(I)

en donde el anillo A, Ar, R^1, R^2, X, Y, W, Z son de conformidad con la reivindicación 1 (con la condición de que Ar no sea un anillo benceno no sustituido),
o una de sus sales, caracterizado porque excluye los siguientes compuestos:
Ácido (4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acético,
(4-(2-{[(4-clorofenil)sulfonil]amino}etil)-3-{[3-(quinolin-2-ilmetoxi)bencil]oxi}fenoxi)acetato de etilo,
[4-(dietilamino)-2-metilfenil]carbamato de 1-{4-metoxi-2-[(4-vinilbencil)oxi]fenil}etilo,
N-{2-[4.5-dimetoxi-2-(2-tienilcarbonil)fenil]etil}-N,4-dimetilbencensulfonamida,
N-(2.2-dimetoxietil)-N-{3-[6-({(2.2-dimetoxietil){(4-metilfenil)sulfonil]amino}metil)-2.3-dimetoxifenoxi]-4-metoxibencil}-4-metilbencensulfonamida, y
Fenilcarbamato de 2-[2-(3.4-dimetoxifenil)etil]-4.5-dimetoxibencilo.

5.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Ar es un anillo aromático monocíclico opcionalmente sustituido, o una de sus sales.

6.- El compuesto de conformidad con la reivindicación 4, caracterizado porque Ar es un heterociclo aromático monocíclico de 5 ó 6 miembros opcionalmente sustituido, o una de sus sales.

1262

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 08 - 11,298
FECHA : FEBRERO 11 DE 2008

No. 08-023022- -00000-0000
Fecha: 2008-03-04 16:30:56 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1262

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678193	11/02/2008	51,814,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Solo 14656-841032-9

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 1263

2020
Bogotá D.C.,

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	8 23022
	Solicitud internacional	PCT/JP2006/316068
	Fecha inicio fase nacional	10/03/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5824
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 08 ABR. 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

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